

# Autoimmune Disorders and Lymphomas

Dolcetti R.<sup>1</sup>, Ponzoni M.<sup>2,3</sup>, Mappa S.<sup>2,4</sup> and Ferreri A.J.M.<sup>2</sup>

<sup>1</sup>*Cancer Bioimmunotherapy Unit, Dept of Oncology,  
National Cancer Institute CRO-IRCCS,*

<sup>2</sup>*Unit of Lymphoid Malignancies, Dept of Onco-Hematology,*

<sup>3</sup>*Pathology Unit, <sup>4</sup>Internal Medicine Unit; San Raffaele Scientific Institute  
Italy*

## 1. Introduction

Patients affected by autoimmune diseases have demonstrated an increased risk of developing lymphoid malignancies. Non-Hodgkin lymphomas (NHL) have consistently been associated with several autoimmune conditions, such as, by way of example, rheumatoid arthritis (RA), Sjögren syndrome (SS) and systemic lupus erythematosus (SLE). Similarly, even if based on fewer studies, an increased risk of malignant lymphomas has also been associated with celiac disease, dermatitis herpetiformis, Hashimoto's thyroiditis, and autoimmune haemolytic anemia. An association between other autoimmune conditions, such as inflammatory bowel diseases (Crohn's disease and ulcerative colitis), psoriasis and systemic sclerosis, and a higher risk of lymphoproliferative disorders has not been consistently proven (Askling *et al*, 2005, von Roon *et al*, 2007, Boffetta *et al*, 2001, Gelfand *et al*, 2006, Chatterjee *et al*, 2005). The magnitude of these associations varies widely among different studies. Reported relative risk is about two-fold in RA, 9-18 fold in SS, 3-6 fold in SLE, celiac disease and Hashimoto thyroiditis, and 2-10 fold in dermatitis herpetiformis. Epidemiologic analysis by NHL subtype have shown that diffuse large B-cell lymphoma (DLBCL) is more frequently associated with RA and SS, while extranodal marginal zone lymphoma, in the respective target organs, is strongly associated with SS (Theander *et al*, 2004) and Hashimoto's thyroiditis. Celiac disease is associated with a 520-fold increased risk of enteropathy-associated T-cell lymphoma of the small intestine (EATL). Autoimmune conditions of the skin including psoriasis, pemphigus and discoid lupus erythematosus have an increased risk of T-cell cutaneous lymphoma (Anderson *et al*, 2009). Hodgkin lymphoma has also been associated with some autoimmune conditions, such as RA, SLE and scleroderma. On the other hand, it is still unclear why other autoimmune conditions, such as type 1 mellitus diabetes, multiple sclerosis, and sarcoidosis do not present an increased risk of lymphoma development. The exact mechanism of lymphomagenesis in the contest of autoimmunity remains largely unexplained, but it may be related to chronic antigenic stimulation, chronic inflammatory response and deficiency in immunosurveillance, promoting a multistep process of genetic instability resulting in accumulation of genetic alterations. In addition, immunosuppressive medications (e.g., methotrexate) may concur to alter patient's immune status. In this chapter, we review the mainstream of epidemiologic studies, discuss the pathways underlying autoimmunity and

lymphomas as well as mechanisms of lymphomagenesis, and summarize the characteristics of the various autoimmune diseases that may be associated with lymphoma. Therapeutic options for these clinically intriguing conditions are also discussed.

## 2. Epidemiologic studies

The first report of an association between autoimmunity and lymphomas was made in 1966 (Mellors, 1966). Notwithstanding the low incidence of autoimmune and lymphoproliferative disorders in the general population, large patients groups and long observation periods are needed to establish an association between these two conditions. In the past, many population-based case-control and cohort studies were carried out to confirm the consistence of an association between these two diseases. Registry-based cohort studies, which are generally based on hospital discharge diagnosis records, are able to evaluate large cohort of patients affected by different autoimmune disorders following them for the occurrence of cancer, usually using cancer registries. This method allows studying large number of patients with autoimmune diseases although lymphoma occurrence is a rare event. Despite the adequate statistical power of these studies, they may over select patients with severe disease, missing patients who are treated only as outpatients. On the other hand, case-control studies of lymphoma patients allows the evaluation of large numbers of well-characterized cancer cases, providing for a wider range of information about lymphoma subtype and covariate exposure of interest, with the disadvantage of rarity of some autoimmune disorders, the low statistical power and control selection bias. Therefore, both study designs have limitations in evaluating the consistence of this peculiar association. Another important limitation of these studies is the potential bias due to reverse causality (i.e., undiagnosed lymphoma causing paraneoplastic inflammation misclassified as rheumatic disease). Many studies have reported in fact a major risk of lymphoma development during the first year after diagnosis of autoimmune disease or have excluded from analysis this time interval. A meta-analysis of all previous available cohort studies relating SLE, RA and SS to the risk of NHL development showed that NHL is more frequent in patients affected by autoimmune diseases than in the general population, especially for SS and SLE (Zintzaras *et al*, 2005). Importantly, a reason for the inconsistent associations between many autoimmune conditions and NHL overall risk may lie in the molecular, morphologic and etiologic heterogeneity of the different NHL subtypes. One of the largest epidemiologic study published has performed a pooled analysis of self-reported autoimmune conditions and NHL different subtypes, including 29,423 participants in 12 case-control studies over Europe, North America and Australia (Ekstrom Smedby *et al*, 2008). The study concluded that an increased risk of NHL is associated only with few autoimmune disorders and that these associations are stronger for some lymphoma subtypes than others. In fact, a 6.5-fold increased risk of NHL was associated with SS, which is lower than in previous reports including only cohorts of hospitalized patients that may present a more severe form of disease. It has been observed a 250-fold increased risk of parotid gland NHL and a 1.000-fold increased risk of marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT)-type of the parotid gland and an association with DLBCL. SLE has been associated with a 2.7-fold increased risk of NHL, in particular, DLBCL and MALT lymphomas. Haemolytic anaemia has been associated with DLBCL. In patients with celiac disease, an increased overall risk for NHL was not observed; only associations with enteropathy-associated T-cell lymphoma of small intestine and anaplastic

large T-cell lymphoma have been detected. Regarding RA, an overall increased risk of NHL was not observed, but only a moderately increased risk in patients treated with corticosteroids or immunosuppressant. Finally, inflammatory bowel disorders, type I diabetes, sarcoidosis, pernicious anaemia, and multiple sclerosis were not associated with increased risk of NHL. Importantly, this analysis demonstrated a persistent risk of lymphoma development also after ten year of autoimmune disease duration, excluding the risk of autoimmune phenomena triggered by yet undiagnosed lymphomas. Another large population-based case-control study from the U.S. Surveillance Epidemiology and End Results-Medicare database has been conducted on 44,350 lymphoid malignancy cases (> 67 years) and 122,531 population-based controls (Anderson *et al*, 2009). Association between specific lymphoid malignancy subtypes and various autoimmune conditions has been also investigated. Although the study was limited to subjects over age 65, the strongest association by NHL subtype was observed between DLBCL and RA and SS; T-cell lymphoma and haemolytic anaemia, psoriasis, discoid lupus erythematosus, and celiac

Studies	Disease	NHL	95% CI	HL	95% CI	<i>p</i>
Zintzaras, 2005	Reumatoid arthritis	3.9 (SIR)	2.5-5.9	-	-	-
	Systemic lupus erythematosus	7.4	3.3-17	-	-	-
	Primary Sjögren syndrome	18.8	9.5-37.3	-	-	-
Engels, 2005	Reumatoid arthritis	1.3 (OR)	0.8-2.1	-	-	0.24
	Systemic lupus erythematosus	1.3	0.3-5.6	-	-	0.72
	Primary Sjögren syndrome	4.9	0.6-43	-	-	0.11
Landgren, 2006	Reumatoid arthritis	-	-	2.7 (OR)	1.9-4.0	-
	Systemic lupus erythematosus	-	-	5.8	2.2-15.1	-
	Systemic scleroderma	-	-	0.6	0.1-6.2	-
	Hashimoto thyroiditis	-	-	2.0	0.3-14	-
Ekstrom Smedby, 2008	Reumatoid arthritis	1.06 (OR)	0.87-1.29	-	-	< 0.1
	Systemic lupus erythematosus	2.69	1.68-4.3	-	-	0.39
	Primary Sjögren syndrome	4.75	1.79-12.6	-	-	0.93
	Secondary Sjögren syndrome	9.57	2.9-31.6	-	-	-
Anderson, 2009	Celiac disease	1.5	0.89-2.54	-	-	0.72
	Rheumatoid arthritis (OR)	1.2	1.1-1.3	1.5 (OR)	1.1-2.0	-
	Systemic lupus erythematosus	1.5	1.2-1.9	3.5	1.9-6.7	-
	Sjögren syndrome	1.9	1.5-2.3	1.6	0.6-4.4	-
	Systemic scleroderma	1.4	0.9-2.2	2.5	0.6-10	-
	Hashimoto thyroiditis	1.1	0.8-1.4	2.1	1.0-4.8	-
	Celiac disease	1.5	0.9-2.5	-	-	-

Table 1. Epidemiologic studies

disease; marginal zone lymphoma and SLE and haemolytic anaemia; Hodgkin lymphoma (HL) and SLE. Additional analysis excluding data for up to 5 years before the diagnosis of malignancy have been also performed to exclude reverse causality, i.e., lymphoma causing autoimmune disorder. Another population based case-control study disclosed a solid association between NHL and SS and a small increase in NHL risk associated with SLE (Engels *et al*, 2005). While most epidemiologic studies demonstrated a consistent association between autoimmunity and NHL, there are only limited data on the risk of developing HL in these settings. A population-based case-control study during a 40-year period analyzed the association between 32 autoimmune disorders and risk of developing HL (Landgren *et al*, 2006), reporting a statistically significant increased risk to develop HL in patients with personal history of RA, SLE, sarcoidosis, or ITP. In addition, personal or family history of sarcoidosis and ulcerative colitis was associated with significantly increased risk of HL.

### 3. Pathogenesis

The aetiology of NHL remains largely unexplained, but some well-established risk factors have been identified. Under normal conditions, B and T lymphocytes respond to antigenic stimulation in a regulated manner and proliferative responses are self-limited. Immune dysregulation, leading to a continue lymphocyte proliferation, is considered to play a major role in lymphomagenesis, as demonstrated by an increased risk of lymphoma development in states of immunosuppression (i.e. following organ transplant or hereditary and acquired immunodeficiency syndromes). In addition, the occurrence of specific subtypes of NHL in

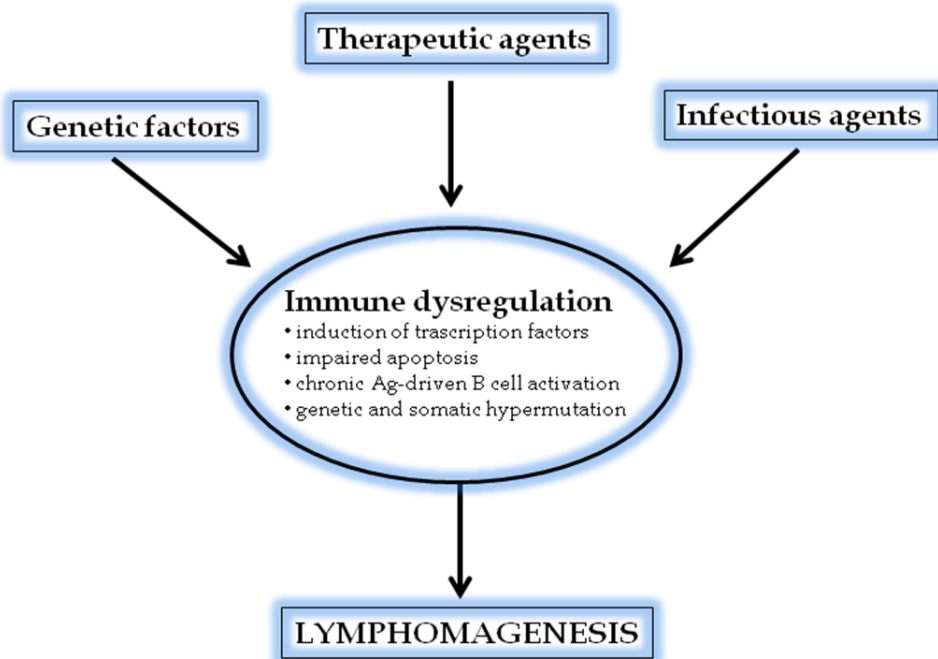


Fig. 1. Proposed pathogenetic factors of lymphomagenesis in the context of autoimmunity

the context of infectious conditions suggests a pathogenic role also for inflammation and chronic immune stimulation. Autoimmune diseases have been considered a possible predisposing factor for lymphoma development as they are characterized by impairment of immune responses leading to a loss of tolerance to self-antigens, a deregulated lymphocyte reactivity with production of autoantibodies against specific tissues and organs. It is conceivable that a sustained antigen-driven B proliferation may increase the risk of adverse genetic events that may finally result in the emergence of a neoplastic clone.

### 3.1 Immune dysregulation

In the development of lymphoma at primary sites, such as MALT lymphomas arising in the parotid gland during the course of SS or in the thyroid gland in the case of chronic thyroiditis, and as T-cell lymphoma in small intestine of patients with celiac disease, a critical role is played by local chronic antigen-driven stimulation leading to the genesis of organized lymphoid tissue, the so called “tertiary” lymphoid tissue, characterized by organ-specific T- or B-cell proliferation, polyclonality and, eventually, oligo-monoclonality.

#### 3.1.1 Tertiary lymphoid tissue

Chronic inflammatory infiltrates resembling the secondary lymphoid organs have been previously described as “tertiary lymphoid organs” (Picker, 1992) and can be induced by the same mediators of lymphoid ontogenesis, such as tumor necrosis factor (TNF)-beta and other members of the TNF family (Kratz *et al*, 1996), through induction of transcription factors, adhesion molecules, lymphoid-tissue-homing chemokines, and other cytokines (Hjelmstrom, 2001). The transcription factor named nuclear factor kappa-B (NF- $\kappa$ B) is induced by TNF proteins and is involved in lymphoid tissue development through chemokines, adhesion molecules and members of the TNF family themselves. TNF proteins are also required for the normal expression of CXCL13 and CCL21, two homing chemokines crucial for lymphoid neogenesis (Ngo *et al*, 1999). CXCR13 is normally produced by stromal cells in lymphoid tissues and attracts naive B cells and activated and memory T cells *in vitro* (Legler *et al*, 1998). CCL21 is a ligand for the CCR7 receptor that directs the migration of naive T cells and dendritic cells. Expression of CXCL13 and CCL21 has been found in disease models of chronic inflammation characterized by lymphoid neogenesis (Hjelmstrom, 2001). Chronic autoimmune diseases are characterized by a chronic inflammatory infiltrate in the target organs, with mononuclear cells and lymphoid follicles. The thyroid gland in patients affected by Hashimoto’s thyroiditis is organized in a structure that resembles a lymph node, including germinal centres, plasma cells and high endothelial venules (Knecht *et al*, 1981, Kabel *et al*, 1989). Also the thymus of patients affected by autoimmune myasthenia gravis is characterized by the presence of ectopic lymphoid follicles with germinal centres containing activated B lymphocytes and plasma cells that produce autoantibodies (Soderstrom *et al*, 1970, Leprince *et al*, 1990). SS is characterized by the presence of antigen-driven proliferation of B cells and lymphoid follicles with clonally expanded lymphocytes (Freimark *et al*, 1989, Stott *et al*, 1998). Similarly, there is an evidence for lymphoid neogenesis in the chronic synovial inflammation of patients with RA (Watson *et al*, 1994, Randen *et al*, 1995); B cell diversification, somatic hypermutation and plasma cells development occur in the synovial germinal centres (Schroder *et al*, 1996, Kim *et al*, 1999) and the homing chemokine CXCL13 seems to be present in the synovial follicles of patients with RA (Hjelmstrom, 2001).

Expansion of B self-reactive lymphocytes is normally limited by several checkpoint mechanisms able to prevent the development of both autoimmunity and lymphoma. Both such diseases may be the result of a multistep process which ends up with the elimination of such aforementioned checkpoints. This multistep process regards both inherited and somatic mutations of genes involved in these pathways. For example, germinal and somatic mutations of *Fas* are associated with both autoimmune diseases and lymphoproliferative disorders, probably by inhibition of apoptosis. Somatic mutations occur physiologically in lymphocytes, during the course of somatic hypermutation of immunoglobulin genes in the germinal centre of lymphoid follicles of lymph nodes and spleen. VDJ recombination, isotype switching and somatic hypermutation, requiring double strand break and DNA rejoining, are susceptible to error and are known to activate oncogenes and inactivate tumour suppression mechanisms. Secondly, the epidemiological evidence of overlapping pathogenesis between autoimmunity and lymphoma may be explained by an enhanced lymphocyte proliferation resulting in increased rates of somatic mutations (Goodnow, 2007). Acquisition of distinct chromosomal translocations among reactive B cells, such as the t(11;18) in the course of *Helicobacter pylori*-positive chronic gastritis, is known to promote lymphomagenesis. Conversely, a similar risk was not found in other settings characterized by chronic immune responses, such as allergic diseases (Soderberg *et al*, 2006) or inflammatory bowel disease (Smedby *et al*, 2006).

### 3.1.2 Triad autoimmunity-lymphoproliferation-lymphoma in Sjögren's Syndrome

Among all autoimmune diseases, SS better reflects the mechanism of the triad autoimmunity-lymphoproliferation-lymphoma. The underlying chronic inflammation, in fact, promotes the formation of organized lymphoid tissue, with a crucial role played by TNF-beta, characterized by the presence of high endothelial venules, dendritic cells and follicular dendritic cells, antigen-driven clonal proliferation of B cells, and lymphoid follicles with clonally expanded lymphocytes (Stott *et al*, 1998, Harris, 1999). The SS-associated chronic lymphoproliferation varies from benign to MALT-type lesions, MALT lymphomas, and even aggressive lymphomas (Burke, 1999). In fact, chronic antigen-driven polyclonal B-cell activation in SS seems to support selection and expansion of auto-reactive B-cell clones through the processes of class switch recombination and somatic hypermutation (Stott *et al*, 1998). Subsequent studies confirmed the selective accumulation of a B cell population characterized by a high rate of mutations in productively rearranged VL chain genes (Jacobi *et al*, 2002, Gellrich *et al*, 1999). The genetic instability associated with DNA hypermutation can favour the escape of malignant B cell clones with the consequent development of an overt B-cell lymphoma (Royer *et al*, 1997). The processes of class switch recombination and somatic hypermutation seem to critically depend on the enzyme activation-induced cytidine deaminase (AID). It has been shown (Bombardieri *et al*, 2007) that AID deaminase is expressed within follicular dendritic cell networks of the salivary gland of patients with SS, in a comparable way to that of secondary lymphoid organs, supporting the hypothesis that ectopic lymphoid tissue recapitulates the molecular setting necessary for local autoantibody production and B-cell expansion. The evolution of a non-malignant B-cell clone present in the parotid gland of a single patient with SS followed at multiple time points over a 7-year period to overt B-cell lymphoma has been documented (Gasparotto *et al*, 2003). In this case, lymphoma evolution occurred in a different site (lung) from that of the primary localization of B-cell proliferation (parotid gland), providing evidence that the pulmonary neoplastic

clone derived from the salivary gland clone, possibly through the acquisition of oncogenic alterations in cell regulatory genes able to confer a more aggressive phenotype.

### 3.1.3 BAFF deregulation and apoptotic resistance

Whether local antigen-driven stimulation and chronic inflammatory processes are important for the development of distant (typically nodal) NHL such as DLBCL is not yet known. Disease severity and inflammatory load are important determinants of NHL development in SS and RA (Theander *et al*, 2006, Baecklund *et al*, 2006a), with an increased risk of occurrence of DLBCL in these autoimmune disorders (Smedby *et al*, 2008), including factors related to cytokine profile, T cell subset balance and apoptotic resistance (Theander *et al*, 2006, Eguchi, 2001). In RA and SLE, apoptotic resistance is increased and mediated by *Bcl-2* expression, activation of NF- $\kappa$ B by inflammatory cytokines and growth factors, and abnormalities in the expression of B-cell activating factor (*BAFF*) (Eguchi, 2001, Mackay *et al*, 2005). *BAFF* is a critical regulator of B-cell homeostasis, and its excessive production causes multiple autoimmune symptoms in mice models and compromises apoptosis of autoreactive B cells. Deregulated *BAFF* expression has been described to lead to disease progression and perpetuation of humoral autoimmunity. Patients affected by systemic autoimmune diseases, such as SS, RA and SLE, have increased levels of *BAFF* in serum and synovial fluid with respect to healthy people. Moreover, serum levels of *BAFF* in SS correlate with the level of autoantibodies, and with rheumatoid factor in patients with RA. *BAFF* has been therefore proposed to play a major role in the development of SS and to contribute in the development of B-cell malignancies. In SS patients, the overexpression of *BAFF* can cause an excessive immunoglobulin production. In salivary glands of patients with SS, the reduced level of apoptosis among *BAFF*-expressing cells might lead to maintain signalling for tissue-infiltrating B cells to proliferate and to become autoantibody-producing plasma cells, contributing to germinal centres formation and lymphoma development. Finally, mice carrying a *BAFF* transgene become highly susceptible to lymphoproliferation, autoimmunity and lymphoma development (Mackay *et al*, 1999). The possible pathogenetic role of *BAFF* in SS and lymphomagenesis has led to the development of agents neutralizing *BAFF* as a new therapeutic option for such patients (Szodoray & Jonsson, 2005). Belimumab, the fully human recombinant IgG monoclonal antibody to soluble B-lymphocyte stimulator human antibody (anti-Blys; LymphoStat-B) binds soluble *BAFF* and prevents interaction with its receptor (Baker *et al*, 2003). Encouraging results have been reported by two large phase III randomized controlled trials of belimumab versus placebo in seropositive SLE patients with stable disease receiving standard of care treatment. The study showed that belimumab improved several markers of disease activity (in the central nervous system, vascular, musculoskeletal, immunologic and cutaneous) and promoted reduction of average steroid dose compared to placebo. Belimumab also determined significant changes in immunologic parameters, such as reduction of IgG and IgM and autoantibodies, increase in C3 and C4 levels, reduction of circulating CD20+ B cells (Thanou-Stavraki & Sawalha, 2011). In summary, a continuous antigen-driven stimulation in a microenvironment where normal regulatory mechanisms are absent may promote both autoimmunity and lymphoma development.

### 3.2 Genetic factors

Several studies explored the relationship between genetic factors and development of lymphoid malignancies in the different settings of autoimmunity. It has been suggested that

some inherited mutations could be involved in pathogenesis of both diseases. For example, inherited mutations of the *TNFSRF6* gene, which encodes the transmembrane protein *Fas* (CD59), a major mediator of lymphocyte apoptosis, lead to a genetic defect in apoptosis responsible of a familial syndrome called “autoimmune lymphoproliferative syndrome of childhood” (ALPS or Canale-Smith syndrome) characterized by chronic, non-malignant diffuse lymphadenopathy and hepatosplenomegaly together with hypergammaglobulinemia, autoantibodies and/or overt autoimmune diseases. These patients are at high risk of developing lymphomas, almost exclusively of the B-cell immunophenotype (HL, follicular, Burkitt and T-cell rich B-cell lymphoma) (Jackson & Puck, 1999) with an incidence of 13% (6 out of 46) among cases studied at the US National Institute of Health, with intervals from the onset of ALPS of 6-48 years (Mackay & Rose, 2001). However, previous population-based case control studies have failed to demonstrate that a family history of autoimmune disease is a risk factor for lymphoma development. A multicenter US study on 759 patients observed that a family history of dermatomyositis was associated with NHL, but not family history of 14 other autoimmune diseases (Engels *et al*, 2005). A statistically significant increase in risk of HL among patients with a family history of sarcoidosis or ulcerative colitis has been reported, but no association with a family history of other autoimmune conditions has been demonstrated (Landgren *et al*, 2006). Finally, an association between the risk of lymphoma development and a family history of a wide range of autoimmune diseases has not been detected in a population-based case-control study on 24,728 NHL patients (Mellemejaer *et al*, 2008). Likewise, an increased risk of lymphoma occurrence among the first-degree relatives of RA patients has not been proven (Ekstrom *et al*, 2003). Therefore, studies evaluating whether genetic factors play a major role in lymphoma development have failed to prove a consistent association in the context of most autoimmune diseases and available data about inherited mutations are still inconsistent.

### 3.3 Therapeutic agents

The role played by autoimmune disease therapy in the subsequent lymphoma development was extensively analyzed, although with inconclusive results. This seems to be due to a selection bias related to the fact that patients requiring therapy usually show a more aggressive disease. Thus, the comparison between treated and untreated patients may result in a falsely increased treatment-associated risk. Disease modifying anti-rheumatic drugs (DMARDs) such as methotrexate and azathioprine have been suggested to increase the relative risk of malignant lymphoma (Baecklund *et al*, 2006b, Bernatsky *et al*, 2008, Askling *et al*, 2009, Wolfe & Michaud, 2007). However, several large population-based studies failed to demonstrate an increased risk linked to methotrexate *per se* (Baecklund *et al*, 2006b, Mariette *et al*, 2002, Wolfe & Michaud, 2004). Corticosteroids, a mainstream of treatment of inflammatory diseases, have never been consistently associated with lymphoma development (Baecklund *et al*, 2006b). Studies about the relationship between nonsteroidal anti-inflammatory drugs (NSAID) and lymphoma are also inconsistent (Baecklund *et al*, 2006b, Sorensen *et al*, 2003). The only exception is constituted by 8 cases of hepatosplenic  $\gamma\delta$  T-cell lymphoma diagnosed among young patients treated with infliximab or adalimumab for inflammatory bowel disease. All patients were receiving concomitant immunosuppressive therapy with azathioprine or prednisone and it was not possible to ascertain if anti-TNF medication had an exclusive role in the pathogenesis of these lymphomas (Mackey *et al*, 2007). Conversely, although it has not been definitively demonstrated, postponing therapy could contribute to lymphoma



development; this could be due to a chronic worsening of the inflammatory microenvironment promoted by uncontrolled disease. In a population-based case-control study (Smedby *et al*, 2006), an increased risk of lymphoma occurrence was detected in patients with RA treated with NSAIDs, corticosteroids and other immunosuppressants but it was not confirmed in untreated patients. This may be related to the fact that the first cohort of patients had a more severe disease with higher levels of chronic inflammation that contributed to lymphoma development.

### 3.3.1 NSAIDs and steroids

Regular use of aspirin and NSAIDs has been hypothesized to be associated with reduced risk of development of colorectal cancer (RR= 0.5-0.8), and possibly of other cancers as stomach, breast, lung, pancreas, and ovary. Decreased cancer risk may be related to inhibition of prostaglandin synthesis, enhancement of cellular immune response or induction of apoptosis. RA patients, who frequently use long-lasting high doses of both aspirin and other NSAIDs, have a decreased risk of colorectal cancer and possibly female breast cancer (Beauparlant *et al*, 1999). Some prospective cohort and case-control studies analyzed the association between aspirin and non-aspirin NSAID use and risk of NHL with contradictory results. An inverse association was documented in a population-based case-control study (OR=0.72; 95% CI= 0.56-0.91) (Holly *et al*, 1999) and a near significant association between regular use of aspirin and moderate decrease of NHL has also been reported in another hospital-based case-control study in men (OR= 0.82; 95% CI= 0.65-1.04), while women who used acetaminophen regularly experienced a 71% elevation in the risk of B-cell NHL (OR= 1.71; 95% CI 1.18-2.50) (Baker *et al*, 2005). A potential protective effect of analgesic use on NHL risk in women but not in men has also been reported (Beiderbeck *et al*, 2003). Conversely, a positive association between use of aspirin or acetaminophen and NHL has been observed among women, but not among men (RR=1.96; 95% CI=0.56-3.08) in a population-based study (Bernstein & Ross, 1992) and a suggestive positive association has also been reported in a prospective study cohort (RR=1.40; 95% CI= 0.99-1.97). This association was lost when aspirin was evaluated alone (Cerhan *et al*, 2003). Finally, no association between aspirin and other analgesics and lymphoma or leukaemia was observed in two other hospital-based case-control studies (Rosenberg *et al*, 1995, Cartwright *et al*, 1988) and in a large study cohort (Sorensen *et al*, 2003). Although the exact reason of this gender discrepancies is unclear, a different response to pharmacologic agents could be referred to women's lower body weight and high percentage of body fat or to endocrine milieu (Meibohm *et al*, 2002). In fact, clearance of both aspirin and acetaminophen positively correlates with body size and is faster in man rather than women (Miners *et al*, 1986) and some metabolizing enzymes are induced by hormones. Treatment with corticosteroids is one of the mainstems of the management of systemic inflammatory diseases, because of their strong and fast anti-inflammatory effects. A linkage between corticosteroids and lymphoma risk was suspected in some studies (Bernstein & Ross, 1992, Kato *et al*, 2002, Zhang *et al*, 2004), whereas this association was excluded by others (Engels *et al*, 2005, Smedby *et al*, 2006, Beiderbeck *et al*, 2003, Chang *et al*, 2005). For example, a markedly reduced risk of lymphoma associated with steroid treatment has been observed in RA patients, also after adjustment for disease severity (Baecklund *et al*, 2006a). Also a case-control study of 378 patients with RA-associated lymphoma demonstrated that treatment with oral steroids was associated with a 30% reduced risk of lymphoma (OR=0.69; 95%

CI=0.51-0.94); this feature remained also after adjustment for DMARDs treatment, disease activity and use of intra-articular steroids. Moreover, treatment up to 2 years showed no protective effect, while a treatment of more than 2 years was associated with a markedly reduced risk. Analysis by lymphoma subtype showed the strongest association between oral steroids and DLBCL (Hellgren *et al*, 2010b). The reduced lymphoma risk associated with steroid therapy might be explained by a reduced inflammatory activity induced by these drugs. Conversely, a meta-analysis of case-control and cohort studies reported between 1992 and 2006 failed to prove an increased risk of lymphoma development over the last decades during which there has been an increased use of immunomodulatory drugs such as corticosteroids and NSAID, disproving thus any possible link between therapy and cancer (Bernatsky *et al*, 2007).

### 3.3.2 Anti-TNF agents

The use of biologic drugs as antagonists of TNF has been extensively evaluated for safety profile both in randomized (Bongartz *et al*, 2006, Leombruno *et al*, 2009) and observational studies (Wolfe & Michaud, 2007, Setoguchi *et al*, 2006, Askling *et al*, 2005). TNF plays an important role in tumour growth control and host defence, and biologic therapy targeting TNF determines an important immunomodulation, raising thus the concern of a possible increased risk of malignancies in patients treated with anti-TNF antibodies. Regarding short-term cancer risk, meta-analysis of clinical trials suggested an increased risk of cancer development (Bongartz *et al*, 2006, Leombruno *et al*, 2009, Bongartz *et al*, 2009), but observational studies did not confirm these results. Randomized controlled trials provide balanced groups for analysis and a well-selected study population but, on the other hand, considering that the time interval from the onset of cancer until its clinical manifestation is counted in years and not in months, any long-term effect of therapy cannot be correctly estimated using data from clinical trials. In addition, the overall number of cancers in these trials is modest, particularly in the control arm. In a review of data from the MedWatch post-market adverse event surveillance system of FDA, 26 cases of spontaneous lymphoproliferative disorders following treatment with etanercept or infliximab have been reported, with an estimated incidence of 19.9 per 10.000 person-year for etanercept and 6.6 per 100.000 person-year for infliximab (Brown *et al*, 2002). These concerns were confirmed also by a meta-analysis of cancer risk in patients affected by RA treated with infliximab or adalimumab in randomized controlled trials, excluding patients treated with etanercept (Bongartz *et al*, 2006), which reported a pooled odds ratio for malignancy in the TNF treated vs. untreated patients of 3.3 (95% CI 1.2-9.1) in a dose-dependent manner. However, included trials were heterogeneous in terms of disease activity, disease duration and previous or concomitant DMARD treatment and usually lasted between 3 months and 1 year, a relatively short interval for estimating cancer incidence. A subsequent update of this meta-analysis with additional data reported an odds ratio of 2.02 (Costenbader *et al*, 2006). Conversely, these results were not confirmed by another meta-analysis assessing 18 randomized controlled trials for a total of 8.808 RA patients (Leombruno *et al*, 2009). Observational studies provide a major number of patients and longer follow-up, but they have also some limitations. The first one is the non-random assignment to treatment, patients with more severe arthritis being more likely treated, and so that outcome could be related to severity of disease rather than treatment. Other limitations may be due to less selected study subjects and introduced bias such as age, sex, smoking history, disease

activity and baseline use of corticosteroids. Another bias could be introduced by physician's decision not to prescribe anti-TNF treatment to a patient with a history of malignancies. Finally, last reason for the divergence between data from trials and from observational studies is the control chosen in the latter. In fact, patients newly starting therapy with anti-TNF should be compared with patients newly starting therapy with other agents for the same disease (Ray, 2003). In Sweden, patients treated with anti-TNF drugs were included in a regional register since the introduction of etanercept and infliximab in 1999 (Geborek *et al*, 2002). A study comparing 757 patients treated with etanercept or infliximab from 1999 to 2002 with 800 patients who received conventional therapy showed no increased risk in solid tumors in anti-TNF treated patients, but, interestingly, five cases of lymphoma were identified among these patients (1.603 person-year), and, compared with conventional-therapy cohort, the relative risk of lymphoma in patients treated with anti-TNF agents was 4.9 (95% CI 0.9-26.2) (Geborek *et al*, 2005). Lymphoma incidence from follow-up of 18,572 American RA patients compared with general population allowed to detect 29 cases of lymphoma, with an overall relative risk for lymphoma of 1.9 in patients with RA not treated with TNF antagonists and tripled (2.9) in patients receiving treatment with TNF antagonists; 2.6 in those receiving infliximab with or without etanercept; and 3.8 in those receiving etanercept with or without infliximab (Wolfe & Michaud, 2004). The increased risk in the TNF antagonist treated group might be due to the fact that patients with the highest risk of lymphoma received TNF antagonists. Consequently, the authors were unable to conclude whether the increased standardized rate ratios were related to RA or truly associated with the drugs. Additionally, this study was not adjusted for patient characteristics other than age and sex. Analysis of cancer risk in TNF antagonists users using a Swedish registry of anti-TNF treated patients and community-based RA patients detected five cases of lymphoma per 1.603 person-year in the treated group and two cases per 3.948 person-year in the comparison group (Franklin *et al*, 2005). The adjusted hazard ratio for lymphoma was 4.9 in anti-TNF treated group, suggesting a large increase in risk. Again, RA severity in patients never treated with anti-TNF agents may be minor. The comparison between a cohort of 4,160 RA patients treated with anti-TNF agents with 53,067 patients with untreated RA, showed that patients with RA are at increased risk of lymphomas in line with previous estimations, and using these expected RA rates as reference, that patients treated with TNF antagonists were not at any additional increased lymphoma risk compared with untreated patients (Askling *et al*, 2005). A cohort study using patients with RA treated with methotrexate (MTX) as a control group did not show any significant increase in the risk of cancer in biologic DMARDs users. This particular control group has been chosen because of similar disease severity between patients treated with these two strategies, and investigators have concluded that it is unlikely that RA patients who have received biologic agents have a greater risk of lymphoproliferative disorders compared with those treated with MTX (Setoguchi *et al*, 2006). A single observational study has reported relative risk for cancer occurrence per single anti-TNF agent (infliximab, etanercept, adalimumab), finding a positive association between biologic therapy and skin cancers, but not with other malignancies, with a median time of exposure of 3.0 years, for any of the three agents separately. However, patients were not followed-up from the start of anti-TNF therapy and so any assessment of risk per time since treatment start was not carried out (Wolfe & Michaud, 2007). Finally, the largest population-based study with the longest observation period investigating cancer risks associated with anti-TNF therapy in RA patients has failed

to prove an overall increase of risk during the first 6 years after treatment start and during follow-up time. In fact patients treated with anti-TNF drugs had the same cancer risk of naïve patients and of those starting MTX or DMARDs combination therapy. Incidence or relative risk of cancer does not increase with time nor with duration of active therapy (Askling *et al*, 2009).

Studies	Overall	95% CI	Infliximab	95% CI	Etanercept	95% CI	Adalimumab	95% CI
Wolfe, 2004	1.9 (SIR)	1.3-2.7	2.6	1.4-4.5	3.8	1.9-7.5	-	-
Geborek, 2005	11.5 (SIR)	3.7-26.9	-	-	-	-	-	-
Askling, 2005	1.9 (SIR)	1.7-2.1	-	-	-	-	-	-
Setoguchi, 2006	1.11 (HR)	0.51-2.37	-	-	-	-	-	-
Wolfe, 2007	1.7 (SIR)	1.3-2.2	0.9	0.4-2.1	1.3	0.6-2.8	1.3	0.2-10
Leombruno, 2008	1.26 (OR)	0.52-3.06	-	-	-	-	-	-

Table 2. Lymphoma risk and anti-TNF agents

### 3.3.3 Methotrexate

Methotrexate (MTX) is a widely used DMARD in the context of autoimmune diseases. RA patients treated with MTX may develop a lymphoproliferative disorder (LPD) resembling lymphomas occurring in immunosuppressed patients (Ellman *et al*, 1991, Kingsmore *et al*, 1992, Liote *et al*, 1995). LPD develops in RA patients at a frequency 2.0-5-fold higher than in general population. MTX-LPD is classified along with other iatrogenic immunodeficiency-related LPDs by WHO classification (Swerdlow *et al*, 2008) and, among these, DLBCL accounts for about 50% of cases, with frequent extranodal involvement and HL for 10-20% of cases. MTX-LPD and non-MTX-LPD seem to share similar clinical findings in RA patients, such as sex, age, primary site, stage and outcome (5-year OS: 59% vs. 53%) (Hoshida *et al*, 2007). Conversely, other papers did not confirm increased incidence of lymphoma in MTX-treated RA patients, even after long-term follow-up (Moder *et al*, 1995, Bologna *et al*, 1997, Kremer, 1997, Weinblatt *et al*, 1998). In a prospective series of 18.572 RA patients, treatment with MTX alone has not been associated with an increased standardized incidence ratio for lymphoma with respect to untreated patients (1.7 vs 1.0) (Wolfe & Michaud, 2004). These results confirmed those reported in a 3-year national prospective study on French RA patients treated with MTX. Investigators have found no increase in lymphoma risk among treated patients compared with French general population. However, in the latter study, authors did not even find an increased lymphoma risk in RA patients overall compared to general population (Mariette *et al*, 2002). There are some case reports of lymphoma regression after MTX discontinuation in patients treated for autoimmune diseases (Liote *et al*, 1995, Kamel *et al*, 1993, Salloum *et al*, 1996). Complete remission occurred generally within 4 weeks after discontinuation of MTX and appeared to persist over a median follow-up of 15 months (4-60). On the other hand, partial remission occurred in a time interval longer

than four weeks, often about 2-3 months later (Rizzi *et al*, 2009). Regression of LPD after MTX discontinuation can be considered an evidence of the carcinogenic potential of MTX. This drug in fact is capable to directly induce reactivation of Epstein-Barr virus (EBV) infection with release of virions (Feng *et al*, 2004). An immunodeficient state provides the conditions for the development of lymphoma possibly through the activation of the oncogenic EBV. The EBV positive rate among patients affected by autoimmune disease and lymphoma is about 30% (Hoshida *et al*, 2007, Kamel *et al*, 1993). Moreover, patients affected by RA have an elevated number of EBV-infected circulating B lymphocytes and a major T-cell defect in EBV-specific suppression (Tosato *et al*, 1984). Taken together, the oncogenic role of EBV, the impaired immune response of RA patients to EBV and the additional immunosuppressive effect of MTX may account for EBV-positive lymphoma development in a small number of RA patients treated with MTX (Baecklund *et al*, 1998). The monoclonal antibody rituximab is currently used for the treatment of LPD after allogeneic transplantation. There are still few reports about its use for MTX-LPDs and more studies are warranted to elucidate its potential therapeutic role in this context.

#### 4. Autoimmune entities

	Most frequent subtype	Risk factors
<b>Rheumatoid arthritis</b>	Diffuse large B- cell lymphoma	High inflammatory activity Male gender
<b>Sjögren syndrome</b>	MALT lymphoma	Low serum immunoglobulins levels High serum $\beta$ 2 microglobulin level Disappearance of a positive rheumatoid factor Hypocomplementemia Low CD4 levels Palpable purpura, parotid gland enlargement
<b>Systemic lupus erythematosus</b>	Diffuse large B- cell lymphoma	Autoimmune haemolytic anaemia Leukopenia Chronic thrombocytopenia Salivary gland swellings Pulmonary infiltrates and/or recurrent pneumonia
<b>Hashimoto's thyroiditis</b>	MALT lymphoma and diffuse large B-cell lymphoma	-
<b>Systemic sclerosis</b>	B-cell lymphomas	-
<b>Celiac disease</b>	Enteropathy-type T-cell lymphoma	Inadequate gluten-free diet
<b>Dermatitis herpetiformis</b>	Enteropathy-type T-cell lymphoma	Inadequate gluten-free diet

Table 3. Most frequent histologic subtypes associated with singular autoimmune entities and known risk factors

## 4.1 Rheumatoid arthritis

RA is a multisystem chronic autoimmune disorder affecting joint and almost any organ system, with inflammatory nodules formation, interstitial lung disease and leukocytoclastic vasculitis (Turesson & Matteson, 2004). Several studies have demonstrated that patients with RA have a 2-fold increased risk of developing lymphoma (Ekstrom *et al*, 2003, Franklin *et al*, 2006) and a link between disease severity and lymphoma risk exist (Smedby *et al*, 2006, Baecklund *et al*, 2006a). A nested case-control study performed to determine factors predisposing to lymphoma development in RA patients demonstrated that a high inflammatory activity is the greater risk factor with an odds ratio of 25.8 compared with low inflammatory activity (Baecklund *et al*, 1998). Furthermore, a study on Felty syndrome, a complication of severe RA, reported a 13-fold relative risk for lymphoma compared with that of general population (Gridley *et al*, 1994). Men affected by RA display a higher standardized incidence ratio for the development of NHL and HL than female (Gridley *et al*, 1993). Finally, a personal history of lymphoma in the years preceding diagnosis of autoimmune disease is not more common in patients affected by RA than expected in general population, while the increased risk of lymphoma development occurs in the first 10 years from RA diagnosis. This proves that shared susceptibility or common risk factors are not the major explanation for this increased risk, but it indicates a critical link between the RA disease or its therapy and the subsequent lymphoma development (Hellgren *et al*, 2010a). Interestingly, the reported relative risk rates remained relatively constant over time despite therapeutic changes occurred in RA.

### 4.1.1 Pathogenesis

The increased risk of lymphoma development in RA patients may arise from the interaction of multiple factors: activation of autoimmune B lymphocytes, chronic inflammation, poor EBV control and immunosuppressive therapy (Balandraud *et al*, 2005). It has been hypothesized that a constant immune stimulation of B cells by auto-antigens may result in both synovitis and lymphocyte activation, finally leading to malignant transformation (Symmons, 1985). Evidence of a B-cell activation is derived from the finding of increased levels of B cell activating factors in RA patients, such as Bly and APRIL, which are produced in the synovial lesions and can drive B cell expansion (Mackay *et al*, 2005, Seyler *et al*, 2005). Moreover, several studies have also reported oligoclonal B cell expansion both in the synovium and in the peripheral blood of RA patients (Berek & Kim, 1997). Whether the increased risk is entirely a consequence of the disease and/or of its treatment is not yet fully ascertained. Patients with RA may lack immunocompetence, being more susceptible to lymphoma development, or immunosuppressive treatment may concur to weaken the patient's immune response. Therefore, lymphoma in RA could be due to a too strong or insufficient immunosuppressive therapy (Weyand *et al*, 2006). A matched case-control study on 378 consecutive Swedish RA patients in whom lymphoma occurred between 1964 and 1995 and 378 healthy controls showed that 48% of lymphoma cases were DLBCLs, and, within those, EBV infection was detected in 12% of lymphomas. Approximately half of the patients had received corticosteroids; 44% had received intra-articular injection of steroids; over 70% of patients had been treated with DMARDs, most frequently antimalarial agents; a few patients had received azathioprine (6%) or MTX (6%) and none had received anti-TNF therapy. An increased lymphoma risk was found only in the azathioprine-treated group, while oral steroids proved to reduce this risk (OR 0.6), especially the intra-articular steroid

treatment (OR 0.2). Patients affected both by RA and lymphoma had received similar treatment than those without lymphoma (Baecklund *et al*, 2006a). In a Japanese cohort of RA patients not treated with immunosuppressive drugs, DLBCL was again the most frequently detected histotype and EBV was present in 30% of cases. Four cases were HL, all of them EBV positive (Hoshida *et al*, 2004). The increased risk of NHL development could be referred to the impaired capacity of RA patients to control infection of EBV (Balandraud *et al*, 2005). EBV is an oncogenic herpes virus involved in the pathogenesis of several lymphomas in the context of states of immunodeficiency (Young & Rickinson, 2004, Ambinder, 2003). EBV is not usually found in DLBCL of immunocompetent patients (Ambinder, 2003). EBV-related lymphomagenesis is characteristic in the setting of organ or bone marrow transplantation and congenital or acquired immunodeficiency disorders (Loren *et al*, 2003). Patients affected by RA have an impaired immune response to EBV. High serum titre of anti-EBV specific antibodies have been detected in some RA patients (Alspaugh *et al*, 1981), EBV-specific CD8+ T cells have been found in synovial fluid (Tan *et al*, 2000) and EBV DNA was isolated from the joints of RA patients (Edinger *et al*, 1999). An impaired control of the outgrowth of EBV infected cells in vitro was also observed (Tosato *et al*, 1981). This hypothesis is also supported by studies of EBV load in RA patients. In fact an increase in shedding of EBV in saliva and in the proportion of EBV-infected circulating B cells in RA patients has been shown (Tosato *et al*, 1984, Yao *et al*, 1986). The mean EBV load in peripheral blood of RA patients is more than 8-fold greater than in normal healthy control, similarly to what occurs in transplant recipients (Balandraud *et al*, 2003). Nonetheless, the overall incidence of EBV positivity in NHL reported in previous cohorts is 24% (Baecklund *et al*, 2006a, Mariette *et al*, 2002), too low to entirely justify the increased incidence of lymphomas among these patients.

#### 4.1.2 Lymphoma subtypes

DLBCL is the most common lymphoma subtype in RA patients, with a prevalence of 48%-67% among all NHL (Mariette *et al*, 2002, Baecklund *et al*, 2003), a slightly higher incidence with respect to the general population of western countries, where DLBCL represents the 30-40% of all NHL. DLBCLs can be further subdivided into germinal centre-like (GC) and activated B cell-like subtypes by gene expression profiling, characterized by a different cellular origin and a different prognosis. The majority of RA patients develops a DLBCL of non GC subtype, particular those with a severe and longstanding disease. These lymphomas are characterized by advanced stage at diagnosis, rapid progression and a worse prognosis (5-year OS: 16% vs. 33% for the GC subtypes). In those patients presenting a severe disease and a continuous immune stimulation, the proliferative drive might determine an increased risk of genetic aberrations, particularly in the peripheral activated B cells, the expansion of an uncontrolled peripheral B cell clone and therefore the development of a non-GC DLBCL. Otherwise, alternative pathways are also probably involved in lymphomagenesis, since only a minor proportion of DLBCL are of GC subtype (30%) and other lymphoma subtypes have also been reported in RA patients (Baecklund *et al*, 2006a). The human germinal-centre associated lymphoma protein (HGAL) is a marker of GC B cell derivation, expressed in the cytoplasm of GC lymphocytes and in lymphomas of GC derivation (Lossos *et al*, 2003, Natkunam *et al*, 2005), which inhibits cell migration in normal GC cells and lymphoma cells (Lu *et al*, 2007). HGAL immunoreactivity has been found in 38 (34%) of 111 RA-DLBCLs (Baecklund *et al*, 2006b), a lower proportion than that reported in DLBCL in general (68%)

(Natkunam *et al*, 2005), but not surprising given the fact that the majority of RA-DLBCLs are of the non-GC type. HGAL expression has been associated with a limited-stage disease and better survival. The expression of HGAL as a GC marker may thus be associated with a better clinical course in RA-DLBCLs.

## 4.2 Sjögren Syndrome

SS is a chronic systemic autoimmune disease clinically characterized by dry mouth (xerostomia) and dry eyes (keratoconjunctivitis sicca) (Kassan & Moutsopoulos, 2004). It is distinguished by a lymphoproliferative sialadenitis (LESA) with lymphocyte infiltration of salivary ducts, ductal epithelial cell proliferation and apoptosis (Daniels, 1984). This disorder can occur either alone, known as primary SS, or in the context of other systemic autoimmune disorders, such as RA, systemic sclerosis, SLE, which is known as secondary SS. Compared with the general population, an increased risk of developing NHL during the course of such disease was reported (Kassan *et al*, 1978, Ioannidis *et al*, 2002). Patients affected by SS, in fact, have an increased relative risk of 28 fold to develop extranodal MALT lymphoma (MZL) of the salivary gland and a 11-fold increased risk of developing a DLBCL arising *de novo* or by transformation of a previous indolent lymphoma (Smedby *et al*, 2006). Relative risk to develop a lymphoma is 8.7 for patients with primary SS form and 4.5 for patients with a secondary SS (Kauppi *et al*, 1997). NHL is the major complication during the course of the disease, with a prevalence of 4.3% (Voulgarelis *et al*, 1999). The high risk of lymphoma development suggests that it originates locally as a consequence of chronic lymphocyte activation due to the autoimmune setting.

### 4.2.1 Pathogenesis

Lymphocytes have a central role in the pathogenesis of both SS and lymphoma, but whether T or B lymphocytes play the leading role is controversial. From one side, biopsies of salivary and lachrymal glands are characterized by a mixed infiltrate of predominant CD4 and CD8 T cells, showing restriction of TCR usage (Adamson *et al*, 1983). On the other side, primary SS is characterized by increased monoclonal Ig and by the development of lymphomas of B-cell type. A B-cell mediated autoimmune response occurs in the salivary glands. A wide variety of nuclear auto-antigens are immune targets in SS patients. Anti-nuclear antibody as anti-SSA/Ro and anti-SSB/La are detectable in 70-85% of patients (Jonsson *et al*, 2003). The cause of B-cell hyperactivity in primary SS is not known. Exocrine glands of SS patients show an accumulation of B cells clustering in benign polyclonal aggregates (Brandtzaeg & Johansen, 2005), harbouring mutated IgVH genes and therefore being GC, marginal zone or memory B cells. Successively, an evolution from benign to malignant B lymphoproliferation has been described in the course of primary SS, but not of secondary (Anderson & Talal, 1972). Initial benign polyclonal clusters of B-cells enlarge to organize lymphoid follicle-like structures with germinal centres (GCs), in which plasma cells differentiate. The role of local antigens is crucial for the development of these extralymphoid GCs (Youinou *et al*, 2010). The evolution from a benign B-cell aggregate to a malignant lymphoma may be therefore the consequence of the autoimmune response through the selection and expansion of a monoclonal B-cell clone (Friedman *et al*, 1991). Mutations of *p53* are also involved in lymphoma development in these patients (Tapinos *et al*, 1999). Approximately 20% of SS patients exhibits monoclonal Igs in the serum and urine and mixed monoclonal



cryoglobulinemia (MMC) with an IgMk monoclonal rheumatoid factor (RF) component (Youinou *et al*, 1988, Tzioufas *et al*, 1986). Monoclonality therefore correlates with the transition from the autoimmune state to NHL. Various studies on clonality have demonstrated that SS patients with the same and persistent monoclonal B-cell expansion in follow-up biopsies are at higher risk of lymphoma developing. MALT lymphoma cells are found only in glands for years and a subsequent spread outside the salivary may involve the lymph nodes and other extranodal organs (Royer *et al*, 1997).

#### 4.2.2 Clinical characteristics

The development of a malignant lymphoproliferation occurs only in a subset of SS patients and is characterized by the emergence of clinical and serologic parameters in the initial phases of disease, the monitoring of which is important for early detection of malignancy and timely therapeutic intervention (Tzioufas *et al*, 1986, Moutsopoulos *et al*, 1983). Usually, median age at lymphoma diagnosis is 58 years, and the median time from SS diagnosis is 7.5 years (Voulgarelis *et al*, 1999). MZL is the most common histologic subtype, but also follicular lymphoma, lymphoplasmacytoid lymphoma and DLBCL have been reported (Kassan *et al*, 1978, Valesini *et al*, 1997, Mariette, 1999). MZL in SS patients is generally localized at diagnosis (stage I and II) and is characterized by a small tumour burden, good performance status and normal lactate dehydrogenase serum levels. The salivary glands are the most commonly involved organs, with parotid gland enlargement being the main presenting symptom, but near 20% of these lymphomas involve other extra-nodal sites, such as stomach, nasopharynx, skin, liver, kidney, and lung, justifying indeed the importance of a complete staging at diagnosis. Bone marrow involvement is rare (10% of cases) and B symptoms are uncommon. Other clinical manifestations are skin vasculitis, peripheral nerve and renal involvement, anemia, lymphopenia, monoclonal immunoglobulins and mixed monoclonal cryoglobulinemia (MMC) (Voulgarelis *et al*, 1999). Indolent lymphomas arisen in SS patients experience high-grade transformation, mostly in DLBCLs, in about 10% of cases. This evolution is characterized by nodal and extra-nodal dissemination and a unfavourable prognosis, with a median overall survival shorter than two years (Voulgarelis *et al*, 1999). It has been proven by immunohistochemical and genotypic studies that such DLBCLs arise from the same clone as indolent lymphomas, as a consequence of genetic alterations such as p53 allelic loss or mutation, hypermethylation of p15 and p16 genes, deletion of p16 gene (Du *et al*, 1996, Neumeister *et al*, 1997).

#### 4.2.3 Risk factors

Some risk factors for lymphoma development have been identified in SS patients. Lymphoma risk seems to increase with disease severity, expressed by decreased levels of serum immunoglobulins, high serum  $\beta$ 2-microglobulin levels and disappearance of a previous positive rheumatoid factor (FR) (Anderson & Talal, 1972, Anaya *et al*, 1996); parotid gland enlargement, splenomegaly, lymphadenopathy (Kassan *et al*, 1978); low C4 levels and palpable purpura (Ioannidis *et al*, 2002, Skopouli *et al*, 2000); MMC (Tzioufas *et al*, 1996). A higher relative risk of developing lymphoproliferative disorders in patients with an early onset of disease has been suggested, with a significant and independent association between lymphoma development and low C4 levels (Ramos-Casals *et al*, 2005). An adverse prognostic value of low levels of C3 (Theander *et al*, 2004), vasculitis, severe involvement in parotid scintigraphy, hypocomplementaemia and/or cryoglobulins at diagnosis (Brito-

Zeron *et al*, 2007) have been proposed in patients with primary SS. Patients with such risk factors should be closely monitored.

#### 4.2.4 Lymphoma treatment

Many patients with localized MALT lymphoma may be managed with a “wait and watch” policy, with a median overall survival of 6.4 years (Voulgarelis *et al*, 1999). In a retrospective study (Ambrosetti *et al*, 2004), no difference in outcome between patients treated with surgery, radiotherapy or chemotherapy and those who were not treated has been reported. Single-agent chemotherapy is indicated (alkylating agents; purine analogues; monoclonal antibody rituximab) for multiple extra-nodal disease. The purine analogue cladribine has been associated with a 75% complete remission rate in patients with SS-associated MALT lymphoma (Voulgarelis *et al*, 2002); while the efficacy of the anti-CD20 monoclonal antibody rituximab is controversial (Pijpe *et al*, 2005, Quartuccio *et al*, 2009). Combined chemotherapy (CHOP-like regimens) should be reserved to patients with high tumour burden or aggressive lymphoma. R-CHOP regimen has been associated with complete remission (duration 10-23 months) in four patients with SS-aggressive NHL. Importantly, certain signs and symptoms of MC type II (purpura, peripheral neuropathy and arthralgias) significantly improved with treatment, the levels of circulating cryoglobulins and RF decreased, and C4 levels returned to normal (Voulgarelis *et al*, 2006).

#### 4.3 Systemic Lupus Erythematosus

SLE is a systemic autoimmune disease characterized by variable severity and a multisystem involvement, including cardiovascular, musculoskeletal, excretory, respiratory, and neurological involvement. Prognosis of SLE patients has considerably improved during the last decades, with an increase in 5-year survival from <50% before 1955 to >90% nowadays (Moss *et al*, 2002), due to the use of novel therapeutic options. Nevertheless, the incidence of late complications seems to be increased and mortality due to malignancies remains higher than that of general population (Nossent *et al*, 2007). This could be referred to the common pathogenic pathways in lupus and cancer. Lupus and various malignancies share some risk factors, such as genetic predisposition, viral infections (EBV), hormones (insulin-like growth factor, prolactin, oestrogen, and growth hormone) (Bernatsky *et al*, 2002, Poole *et al*, 2009). Another shared characteristic is represented by antiphospholipid antibodies, frequently present in both diseases and recently associated with cancer development (Tincani *et al*, 2010). SLE has been associated with a 2.7 - 4.1 fold increased risk of NHL development (Ekstrom Smedby *et al*, 2008, Abu-Shakra *et al*, 1993, Ekstrom *et al*, 2003), and some studies have also suggested a link between SLE and HL (Landgren *et al*, 2006, Bernatsky *et al*, 2007). A multi-site international cohort study calculated a standardized incidence ratio (SIR) for all hematologic malignancies of 2.75 and for NHL of 3.64 (Bernatsky *et al*, 2005b). As far as HL, same authors observed a SIR of 2.4 in another large multi-site international cohort (Bernatsky *et al*, 2007). The pooled analysis combining these data with those of other large cohort studies provided a SIR estimate for HL in SLE of 3.16. Generally, aggressive lymphomas, such as DLBCL are more common in SLE patients (Smedby *et al*, 2006, Simon *et al*, 2007, Bernatsky *et al*, 2005a, Lofstrom *et al*, 2007). In general population, DLBCL accounts for 30% of all lymphomas, but in SLE patients this percentage is between 38% and 64% (Smedby *et al*, 2006, Bernatsky *et al*, 2005a, King & Costenbader, 2007). No subtyping into germinal-centre like or activated B-cell like subtype has been reported.

### 4.3.1 Pathogenesis

Concerning genetic predisposition, a possible reason for the increased risk of NHL in SLE is that distinct major histocompatibility complex (MHC)-haplotypes may predispose to both disorders (Okada *et al*, 1991). The role of immunosuppressive therapy is controversial; it may impair immune defence resulting in an increased risk of lymphomagenesis. However, SLE patients who have never been treated with immunosuppressive agents have the highest rate of NHL incidence during the first year from diagnosis, suggesting that the increased risk is not related to cumulative doses of therapy (Kiss *et al*, 2010). A nested case-cohort study performed to assess the HR for cancer within a multi-site international SLE cohort after exposure to immunosuppressive drugs (anti-malarial drugs, systemic glucocorticoids, NSAIDs, aspirin) showed an adjusted HR for overall cancer risk of 0.82. This risk seems to be higher when only haematological malignancies are considered (Bernatsky *et al*, 2008). In addition to extrinsic risk factors, there are also defects in the immune system contributing to the development of both SLE and lymphomas, as the abnormal B-cell activation due to the chronic and persistent antigen-stimulation, cell-cycle deregulation and impaired apoptosis, which leads to uncontrolled cell proliferation, an exaggerated humoral autoimmune response and the increased risk of oncogene translocation (Illes *et al*, 2009). The impaired immune response in SLE is thus characterized by the accumulation of activated self-reactive B and T cells (Xu & Wiernik, 2001). Many studies have underlined the role of impaired apoptosis in this process. For example, the MRL/lpr mouse, a murine SLE model, has defects in the *Fas* gene, leading to defects in apoptosis and subsequent development of SLE (Watanabe-Fukunaga *et al*, 1992). Mice with mutations of *PTEN*, a tumor suppressor gene, which impairs the *Fas*-mediated elimination of activated lymphocytes, develop SLE characterized by ANA antibodies, glomerulonephritis and lymphadenopathies (Di Cristofano *et al*, 1999). Also *bcl-2*, a proto-oncogene involved in the majority of B NHL, is highly expressed in SLE (Aringer *et al*, 1994), causing prolonged survival of auto-reactive B cells and thus favouring malignant transformation (Xu & Wiernik, 2001). The persistent clonal expansion of benign hyperactive B and T cells retained in lymph node of SLE patients in response to self-antigens exposes these cells to DNA damage, ultimately leading to neoplastic transformation (Xu & Wiernik, 2001). Increased serum levels of type-I Interferons (IFNs a/b) is also associated with active SLE disease (Theofilopoulos *et al*, 2005). The IFNs are cytokines that inhibit cell proliferation and modulate cell survival (Banchereau & Pascual, 2006), and also inhibit apoptosis induced by signalling through B-cell receptor (Su & David, 1999). The p202a murine protein is a member of the interferon-inducible p200-protein family (Choubey & Kotzin, 2002). Increased levels of the p202 protein in splenic B cells of B6.Nba2 SLE susceptible mice determine defects of apoptosis and accumulation of B cells in the spleen (Xin *et al*, 2006) probably by inhibiting p53-mediated transcriptional activation of genes that encode pro-apoptotic proteins as well as transcriptional repression of genes that encode anti-apoptotic proteins. It is therefore possible that increased levels of p202 in B cells also contribute to enhance the risk of developing B-cell malignancies (Veeranki & Choubey, 2010). The murine p202 protein does not have any human homologue, but the human IFI16 protein, a member of the p200-protein family, is functionally similar. An increased expression of IFI16 protein in normal human cells determines cellular growth arrest and up to 29% of SLE patients present high auto-antibodies titres to the IFI16 protein (Choubey *et al*, 2008). IFI16 protein binds p53, so basal and IFN-induced increased levels of IFI16 in SLE patients may inhibit the p53 mediated

transcription of target genes (Choubey *et al*, 2008). Finally, SLE patients have high plasma levels of BAFF (Do & Chen-Kiang, 2002), which activates NF- $\kappa$ B (Laabi & Strasser, 2000). Mice overexpressing BAFF develop a SLE-like disease and exhibit B-cell activation (Mackay *et al*, 1999). Also the increased level of IFI16 protein in B cells is capable to activate the NF- $\kappa$ B transcription factor, which persistent activation has been related to the development of B cell malignancies (Vallabhapurapu & Karin, 2009). In addition, NF- $\kappa$ B induces IL-6 expression (Choubey & Panchanathan, 2008). Overall, these results suggest that the triad IFI16/NF- $\kappa$ B/IL-6 could be involved in the development of B-cell malignancies in SLE patients. Recently, it was also shown that antiribosomal-P-protein (anti-P) antibodies, present in nearly 15-20% of patients with SLE active disease, cross react with phospholipids (Caponi *et al*, 2007), enhancing the production of TNF- $\alpha$  and IL-6 by monocytes (Toubi & Shoenfeld, 2007), which increases proliferation of normal and clonal B cells. The role of EBV in the pathogenesis of lymphoma in SLE patients has not been fully investigated. An increased prevalence of EBV infection in young patients with SLE has been reported (James *et al*, 1997) and there are some observations that, in some cases, EBV may be a trigger of lymphomagenesis in SLE (Verdolini *et al*, 2002). In contrast, in a retrospective study analyzing lymphoma development in a large cohort of SLE patients, EBV positivity was found only in 17% of cases (King & Costenbader, 2007). Whether EBV infection causes SLE and/or lymphoma independently has not yet been ascertained.

#### 4.3.2 Clinical characteristics

The emerge of NHL in a SLE patient is clinically difficult to recognize in the current practice, due to the fact that many lymphoma characteristics are already part of the autoimmune disease (lymphadenopathy, fever, weight loss, hepato-splenomegaly, cytopenias, autoantibodies), raising the possibility that SLE might be a paraneoplastic syndrome appearing in the context of the lymphoid malignancy. Some clinical SLE characteristics as haematological manifestations (autoimmune haemolytic anaemia, leukopenia, hyperglobulinemia, chronic thrombocytopenia) (King & Costenbader, 2007), sicca symptoms/salivary gland swellings, pulmonary infiltrates, and/or recurrent pneumonia (Lofstrom *et al*, 2007) have been associated with increased risk of developing lymphoma. The common involvement of mucosal membranes, salivary glands and lung parenchyma in patients developing a lymphoma could be due to the fact that, in an immune-deficient patient, an impaired barrier for exogenous agents, as viruses, favour recurrent infections, which may be involved in lymphomagenesis. Median age at lymphoma diagnosis is 50 years, with a median time interval from SLE diagnosis of 17.8 years (King & Costenbader, 2007). Diffuse large B cell lymphoma is the most common subtype (King & Costenbader, 2007). After diagnosis of NHL a 5-year survival probability of 47%-50% has been estimated (Bernatsky *et al*, 2005b, Lofstrom *et al*, 2007), and mortality in patients with both diseases is usually due to progressive B-cell malignancy (Xu & Wiernik, 2001).

#### 4.4 Hashimoto's thyroiditis

Hashimoto's thyroiditis (HT) is an autoimmune chronic inflammatory disease of the thyroid, histologically characterized by a severe and progressive lymphocytic infiltration causing destruction of the glandular parenchyma and consequent goitre development and hypothyroidism. It commonly affects middle-aged women (Aozasa, 1990). The activation of CD4<sup>+</sup> T lymphocytes specific for thyroid antigens is considered the trigger of the autoimmune process in HT (Weetman & McGregor, 1994, Dayan & Daniels, 1996). Auto-

antibodies produced in HT are specific for thyroglobulin, thyroperoxidase and the thyroid stimulating hormone receptor (TSH-R). The first two antibodies are not detected in all patients. Antibodies against TSH-R block the activation of this receptor, causing the functional impairment of the thyroid. On the other side, activated CD4+ T cells recruit cytotoxic CD8+ T cells and B cells into the thyroid causing the direct killing of thyroid cells. Patients affected by HT are at increased risk of developing primary thyroid lymphoma (PTL) with a relative risk of 67 fold for marginal zone B-cell lymphoma of MALT-type (Holm *et al*, 1985). Lymphoma typically occurs 20-30 years after the diagnosis of thyroiditis (Pedersen & Pedersen, 1996). HT is not only associated with thyroidal MALT lymphoma, but also with other extranodal lymphomas. In a retrospective study on 80 patients affected by MALT lymphoma, 13 (16%) had a concomitant diagnosis of HT; four of these patients had thyroidal lymphoma and nine had extra-thyroidal lymphomas (gastric, orbital, small intestinal, and salivary gland lymphomas) (Troch *et al*, 2008). PTL represents 5% of all thyroid malignancies (Staunton & Greening, 1973) and MALT lymphoma represent 25% of all PTLs (Thieblemont *et al*, 2002, Derringer *et al*, 2000). About 50% of patients diagnosed with PTL have a clinical history of HT (Niitsu *et al*, 2007, Rossi, 2009), even if only 0.5% of patients with HT develop PTL.

#### 4.4.1 Pathogenesis

It has been hypothesized that the chronic antigenic stimulation caused by the autoimmune and inflammatory process in HT leads to the proliferation of newly formed lymphoid tissue and ultimately to malignant transformation. The thyroid gland does not contain native lymphoid tissue (Holm *et al*, 1985, Isaacson, 1997). The lymphoid tissue present in HT thyroid gland share many features with MALT (Hyjek & Isaacson, 1988). The presence of clonal B-cell populations has been demonstrated in HT thyroid specimens also in patients without evidence of lymphoma development (Saxena *et al*, 2004). The clonal IgH gene rearrangements carried by thyroid lymphomas may already be evident in the oligoclonal rearrangements characterizing HT, and a fraction of thyroid lymphomas use the same IgH utilized by anti-thyroid auto-antibodies (Rossi, 2009, Moshynska & Saxena, 2008). IGVH genes are extensively targeted by aberrant somatic hypermutation in thyroid DLBCL, MALT and follicular lymphoma, and also in 2 of 14 (14.3%) patients affected by HT, suggesting that these genetic alterations represent an early step in the process of B-cell lymphomagenesis. This aberrant activity of somatic hypermutation may introduce activating mutations and may cause genetic instability, favouring chromosomal translocation (Takakuwa *et al*, 2009).

#### 4.4.2 Clinical characteristics

Patients developing a PTL clinically present a rapid growth of a thyroid mass, associated with hoarseness, stridor or, less commonly, with dysphagia or dyspnoea. The presence of B symptoms is uncommon in indolent subtypes (Ansell *et al*, 1999). Up to 90% of patients usually presents with early stage I or II lymphoma (Graff-Baker *et al*, 2010). The most common histologic subtypes are B cell-type, in particular MALT lymphomas and DLBCL. The other histological subtypes are exceptional (Thieblemont *et al*, 2002). MALT lymphoma is an indolent lymphoma, with a 5-year disease-free survival of over 95% (Graff-Baker *et al*, 2010) and the disease tends to remain localized for a long time. Conversely, aggressive DLBCL usually arise from a pre-existing MALT lymphoma and a component of residual MALT lymphoma can be still found (Niitsu *et al*, 2007). DLBCL has a dismal prognosis

despite polychemotherapeutic regimens, with a 5 year probability of survival of 44% (Thieblemont *et al*, 2002). Only rare cases of HL of the thyroid have been reported in the literature, but any association with underlying thyroiditis cannot be ascertained because of the small number of cases (Wang *et al*, 2005). Older age at diagnosis is associated with decreased disease-free survival (Graff-Baker *et al*, 2010). Tissue biopsies should be considered the gold standard for histological diagnosis (Thieblemont *et al*, 2002).

#### 4.4.3 Therapy

Local treatment, such as surgical excision and radiotherapy, could represent a valid treatment strategy for patients with stage I or II MALT lymphoma of the thyroid gland (Tsang *et al*, 2003). Complete surgical resection improves prognosis over incomplete resection, with a 5-year OS of 100% (Thieblemont *et al*, 2002), although most authors currently believe that total thyroidectomy is unnecessary, exposing patients to the risks of surgery (recurrent laryngeal nerve damage and hypoparathyroidism) without conferring any survival advantage (Tupchong *et al*, 1986, Ruggiero *et al*, 2005, Klyachkin *et al*, 1998). Involved field radiotherapy is associated with a 5-year OS of 90% (Laing *et al*, 1994). Nonetheless, patients with thyroid malignant lymphoma treated with radiotherapy seem to have a higher incidence of hypothyroidism than those treated with chemotherapy (Tamura *et al*, 1981). Localized treatment plays a minor role in DLBCL, which requires aggressive anthracycline-based chemotherapy regimens (CHOP or CHOP-like), associated with rituximab, a monoclonal antibody directed against B-cell specific antigen CD20, and followed by involved-field radiotherapy. Chemotherapy alone may be considered in selected patients younger than 60 years and with no adverse prognostic factors (Reyes *et al*, 2005). Rituximab is effective for autoimmune thyroid diseases such as Grave's disease (El Fassi *et al*, 2007a, El Fassi *et al*, 2007b). The use of rituximab monotherapy in three cases of HT-related thyroid MALT lymphoma has also been reported. Rituximab monotherapy determined a significant decrease of anti-thyroid autoantibody levels, but it is still unknown whether thyroid dysfunction can be restored, and its use remains still controversial in HT (Kahara *et al*, 2011).

#### 4.5 Systemic sclerosis

Systemic sclerosis (SSc) is a multisystem inflammatory disease with autoimmune features. It is characterized by vascular abnormalities and fibrosis of the skin and internal organs. Some retrospective studies have reported an increased risk of malignancies in SSc patients (Abu-Shakra *et al*, 1993, Rosenthal *et al*, 1993, Derk *et al*, 2006), but data on the link between SSc and lymphoproliferative disorders are still controversial. This association was first proposed in 1953 (ZATUCHNI *et al*, 1953) and successively several epidemiological studies have been performed to explore this risk (Chatterjee *et al*, 2005, Hill *et al*, 2003, Duncan & Winkelmann, 1979). A number of sporadic case reports have underlined the association between SSc and NHL, particularly with aggressive B-cell subtypes (Arnaud *et al*, 2006, Derk *et al*, 2004, Haviv *et al*, 1997) and some authors observed an increased risk of NHL among SSc patients, primarily within the first year after the onset of disease, but not beyond 4 years of follow up (Landgren *et al*, 2006, Mellemkjaer *et al*, 2008, Rosenthal *et al*, 1993). Conversely, other studies failed to demonstrate a consistent association between SSc and lymphomas (Chatterjee *et al*, 2005, Rosenthal *et al*, 1995, Roumm & Medsger, 1985). In some cases, systemic sclerosis could even represent a paraneoplastic syndrome (Vettori *et al*, 2010). In a

population-based cohort study from south-west England to determine if patients with scleroderma have an increased risk of malignancy compared with general population, the highest risk among patients affected by scleroderma was found for haematological malignancies, especially for NHL (RR=25.8) (Siau *et al*, 2010). Another retrospective analysis of 218 Hungarian patients with SSc followed during a period of 12 years showed lymphoma development in three of them (1.38%), all of B cell phenotype, within 2 years after the onset of SSc. The incidence of lymphoma in this cohort was 38.3 cases per 100.000 patients per year (Szekanecz *et al*, 2008). Considering 24 studies analyzed in a review, characteristics associated to NHL development are old age, female sex, diffuse cutaneous subset and early disease. B-cell lymphoma represents the most frequent histotype and the interval between diagnosis of SSc and lymphoma onset is usually short (Vettori *et al*, 2010). Some sporadic cases have also reported an association with HL (Rosenthal *et al*, 1993, Duggal *et al*, 2002, Kedar *et al*, 1979, Hall *et al*, 1978).

#### 4.5.1 Pathogenesis

The pathophysiological relationship between scleroderma and malignancy remains poorly understood. There might be multiple pathways leading to cancer in general, and lymphoproliferative disorders in particular. B cells have many pathogenic roles in SSc (Sato *et al*, 2004). SSc patients are indeed characterized by alterations of the B-cell homeostasis, such as expansion of naïve cells, decreased number of circulating but activated memory cells and defective natural killer cells activity (Sato *et al*, 2004, Horikawa *et al*, 2005). Therefore, altered B cell functions may be responsible of the higher incidence of B NHL. Also TGF- $\beta$ , a cytokine involved in the regulation of connective tissue proteins, which is highly expressed in SSc tissues, might play an important role since dysregulated signalling of the TGF- $\beta$  is capable to induce tumorigenesis (Grady, 2005). Moreover, the malignant transformation might be a consequence of chronic tissue damage. Finally, EBV-encoded small RNAs have been detected in the majority of DLBCLs associated with systemic rheumatic diseases, including SSc (Kojima *et al*, 2006). In conclusion, a clear relationship between SSc and NHL has not yet been ascertained and further studies with higher number of patients are required to clarify the coexistence of these two entities.

#### 4.6 Celiac disease

Celiac disease (CD) is a chronic autoimmune enteropathy affecting small-intestine, triggered by gluten proteins from wheat, barley and rye. The small-intestinal mucosal injury caused by the autoimmune response determines malabsorption which results in gastrointestinal symptoms (diarrhoea, weight loss, abdominal pain, anorexia, lactose intolerance, abdominal distension and irritability) and/or non-gastrointestinal features (iron-deficiency anaemia, dermatitis herpetiformis, chronic fatigue, joint pain/inflammation, migraines, depression, attention-deficit disorder, epilepsy, osteoporosis/osteopenia, infertility and/or recurrent fetal loss, vitamin deficiencies, short stature, failure to thrive, delayed puberty, dental defects and autoimmune disorders). The diagnosis of CD is based on histologic characteristics of small-bowel biopsy and on clinical and histological remission after a strict gluten-free diet. The presence of circulating CD-associated antibodies, such as IgA against the endomysium of connective tissue and against tissue transglutaminase, at time of diagnosis and their normalization after a gluten-free diet support the diagnosis of CD. Most CD patients display specific pairs of allelic variants in two HLA genes, HLA-DQA1 and

HLA-DQB1. Adhering to a strict gluten-free diet usually results in healing of the damaged small-intestinal mucosa and improvement of intestinal absorption. A gluten-free diet is sufficient to treat the majority of patients. Two–5% of patients with adult-onset CD, especially those diagnosed above the age of 50, does not respond to a gluten-free diet (Tack *et al*, 2010a). Refractory celiac disease (RCD) is defined when clinical and histological symptoms recur after a good response to a gluten-free diet or persist after more than 12 months of strict diet. Patients affected by CD are at increased risk of lymphoma development, not only primary gastrointestinal, but at any site. The occurrence of an EATL is the main cause of death in RCD patient. About 50-60% of patients with RCD type II develop an EATL within 5 years (Al-Toma *et al*, 2007, Di Sabatino & Corazza, 2009, Daum *et al*, 2003). Despite the strong association between CD and EATL, the majority of lymphomas associated with CD are of different histologies, such as DLBCL and peripheral T cell lymphomas (Catassi *et al*, 2002, Mearin *et al*, 2006, Smedby *et al*, 2005, Halfdanarson *et al*, 2010).

#### 4.6.1 Epidemiology

Earlier estimates of risk of NHL in CD amply varies, from no increased risk (Collin *et al*, 1994) to a 42-fold (Holmes *et al*, 1989) or a 69-fold increased risk of NHL (Corrao *et al*, 2001). A significant increased risk of NHL among CD patients has been reported, with a SIR of 2.2 (95% CI 1.3-3.6) for B-cell NHL and 3.6 (95% CI 2.3-5.2) for lymphomas of non-intestinal origin (Smedby *et al*, 2005), most common subtype being DLBCL. The RR for T cell NHL was 50-fold increased. Patients with B-cell lymphomas have been demonstrated to have a better prognosis than those with T cell NHL (Halfdanarson *et al*, 2010). To investigate the frequency of CD among patients with NHL a prospective, multi-centre case-control study was conducted in 10 European countries between 1998 and 2002, showing that patients with CD have a significantly increased risk of developing NHL (OR=2.6 95%CI=1.4-4.9) in comparison with the general population. Importantly, the increased frequency of CD in NHL occurred in those celiac patients diagnosed clinically before screening and not in undiagnosed CD (Mearin *et al*, 2006). Another large nationwide population-based study assessed and compared risk of developing a lymphoproliferative disease among three different classes of subjects: patients affected by CD, patients with small bowel intestinal inflammation and patients with latent CD. It was showed an increased risk of lymphoproliferative malignancy (HR=2.82 95% CI 2.36-3.37) associated with the presence of a biopsy-proven CD, even after 5 years of follow up, but not with latent CD. The increased risk regarded NHL of the T cell and the B cell type as well as HL (Elfstrom *et al*, 2011). The risk of developing a lymphoma in CD patients is related to the age of diagnosis of CD. As a matter of fact, mean age at diagnosis of patients who develops a cancer is higher than that of patients who did not (Silano *et al*, 2007). This could be due to the diagnostic delay causing a prolonged period of dietary exposure to gluten (Holmes *et al*, 1989, Corrao *et al*, 2001). The risk of developing a malignancy in patients with CD who adhere to a gluten-free diet for five consecutive years or more is not increased compared with that of general population (Holmes *et al*, 1989, Lewis *et al*, 1996, Silano *et al*, 2008).

#### 4.6.2 EATL

EATL is an intestinal tumour of intraepithelial T lymphocytes, usually presenting as a neoplasm composed of large lymphoid cells and often associated with necrosis and an



inflammatory background, including large number of histiocytes and eosinophils. The adjacent intestinal mucosa frequently shows enteropathy with villous atrophy, crypt hyperplasia, increased *lamina propria* lymphocytes and plasma cells and intraepithelial lymphocytosis (Chott *et al*, 1998). In 10-20% of cases, lymphoma is composed of monomorphic medium-sized cells with no inflammatory background and rare necrosis (type II EATL) and may occur sporadically, not associated with CD. EATL more often occurs in the jejunum or ileum as one or more ulcerating mucosal lesions that invade the wall of intestine and frequently cause perforation. The time interval between diagnosis of CD and development of lymphoma varies from 2 months to more than 5 years (Ilyas *et al*, 1995). HLA genotyping shows that patients with EATL have the CD-associated DQA1\*0501, DQB1\*0201 phenotype, and additional HLA-DR/DQ alleles may increase the risk of lymphoma (Wright, 1995).

#### 4.6.2.1 Pathogenesis

RCD patients can be classified as RCD type I and type II. Type-II RCD patients have >20% phenotypically aberrant intraepithelial lymphocytes (IEL), expressing cytoplasmatic CD3, but lacking surface expression of CD3, CD4 and CD8, while type-I RCD patients have normal IEL (Cellier *et al*, 2000, Patey-Mariaud De Serre *et al*, 2000). IEL with aberrant phenotype also show monoclonal T-cell receptor (TCR)-gamma rearrangement (Bagdi *et al*, 1999), suggesting that these cells constitute a neoplastic population. Moreover, in those patients with type II RCD who subsequently develop EATL, the IEL share the same monoclonal TCR-gamma as the subsequent T-cell lymphoma (Cellier *et al*, 2000, Cellier *et al*, 1998, Daum *et al*, 2005, Ashton-Key *et al*, 1997) and carry gain of chromosome 1q in common with 16% of EATL (Verkarre *et al*, 2003). Therefore, type II RCD may be considered an example of cryptic intraepithelial T-cell lymphoma (Daum *et al*, 2001). CD30+ IEL in RCD II seem to indicate a worse prognosis, including risk of developing lymphoma (Farstad *et al*, 2002). Also interleukin 15 (IL15) might play a role in lymphomagenesis. Uncontrolled overexpression of IL15 by enterocytes in patients with type-II RCD promotes and maintain activation of IEL, favouring the emergence of T-cell clonal proliferations and the subsequent transformation into EATL (Mention *et al*, 2003).

#### 4.6.2.2 Clinical characteristics and prognosis

EATL often present at older age (mean > 60 years) and in patients with a reduced performance status. In most cases disease is disseminated at diagnosis. Patients generally present with abdominal pain, often associated with jejunal perforation, weight loss, diarrhoea or bowel obstruction. Since obstruction and perforation are frequent, many cases are diagnosed at laparotomy. EATL is characterized by multifocal presentation in 10-25% of cases. Neurologic symptoms are reported in approximately 6% of adults with CD, of which cerebellar ataxia is the most frequent one. EATL is an aggressive malignancy that, if untreated, leads to death due to multifocal intestinal perforation caused by refractory malignant ulcers. The prognosis of EATL is very poor compared with that of intestinal B cell lymphomas (Domizio *et al*, 1993). It shows low chemosensitivity, rapid tumour growth and a tendency to dissemination with about 80% of patients experiencing relapse, even after 5 years of follow up, and a 1- and 5-year survival rates of 31-39% and 8-20% respectively (Al-Toma *et al*, 2007, Daum *et al*, 2003). Overall, the dismal prognosis of these patients reflects in part late diagnosis and in part the poor performance status due to the compromised immunological and nutritional status (Gale *et al*, 2000). Stage is the main prognostic factor,

with a 5-year cause-specific survival higher than 60% for patients with limited disease and 25% for those with advanced stage (d'Amore *et al*, 1994, Chott *et al*, 1992).

#### 4.6.2.3 Therapy

A standard treatment for patients with EATL has not been established, and reported results are overall unsatisfactory. Most patients with EATL are managed with a surgical approach as the primary strategy. Even if surgery is not a curative approach, debulking and resection of masses at high risk of perforation following chemotherapy or occlusion are frequently indicated in these patients. Involved-field radiotherapy 35 Gy was indicated in some patients with bulky disease or incomplete resection (Novakovic *et al*, 2006), but it is used almost exclusively with palliative purposes. Combined treatment modality with debulking surgery followed by systemic anthracycline-containing polichemotherapy, with or without consolidation radiotherapy, showed an ORR of 58%, a 5-year FFS of 3% and a 5-year OS of 20-25% (Domizio *et al*, 1993, Gale *et al*, 2000, d'Amore *et al*, 1994, Morton *et al*, 1993). Many patients are unable to complete the chemotherapy program and do not receive radiotherapy due to rapid disease progression, poor nutritional and performance status, associated with local and systemic complications (Daum *et al*, 2003, Gale *et al*, 2000). Given the dismal prognosis of patients treated with conventional chemotherapy, some authors assessed feasibility and activity of high-dose chemotherapy supported by autologous stem cell transplantation as upfront treatment of EATL, with conflicting results. Most of these studies are based on small retrospective series of patients with disomogeneous characteristics, and utilizing different conditioning regimens (Al-Toma *et al*, 2007, Bishton & Haynes, 2007). High-dose chemotherapy with IVE/MTX (ifosfamide, vincristine, etoposide, methotrexate) followed by ASCT has been associated with significantly better outcome in comparison with historical controls treated with conventional anthracycline-based chemotherapy. In fact, patients treated with IVE/MTX-ASCT had an improved remission rate (69% vs. 42%); lower death rates and higher 5-year PFS and OS (52% vs. 22% and 60% vs. 22%, respectively) (Sieniawski *et al*, 2010). Interestingly, chemotherapy supported by ASCT may also prevent EATL development in patients with RCD (Meijer *et al*, 2004). In fact, in a retrospective series of 18 patients with RCD type II, 13 patients successfully underwent conditioning with fludarabine and melphalan supported by ASCT, with a significant reduction of the aberrant T-cells in duodenal biopsies associated with improvement in clinical well-being and normalization of hematologic and biochemical markers. After a follow up > 2 years EATL developed only in one transplanted patients, with a 4-year survival rate of 66% (Tack *et al*, 2010b). Alemtuzumab, a humanized anti-CD52 monoclonal antibody has been rarely used in EATL. The combination of gemcitabine and alemtuzumab has been successfully used in an elderly patients with poor performance status and extra-intestinal dissemination of EATL both at diagnosis and relapse (Soldini *et al*, 2008). Another patient with EATL was treated with alemtuzumab-CHOP combination at diagnosis in a prospective phase II trial on T-cell lymphomas achieving a short-lasting complete remission (Gallamini *et al*, 2007). Moreover, alemtuzumab was successfully used in the treatment of a patient with RCD at high risk of developing EATL, obtaining a total recovery of duodenal biopsy (Vivas *et al*, 2006). Patients with refractory or relapsed EATL and without formal contraindications should be therefore managed with high-dose chemotherapy supported by ASCT. Two patients in CR were treated with allogeneic SCT with reduced intensity conditioning regimen, with a HLA identical sibling donor. Both patients relapsed within few months after transplantation (van de Water *et al*, 2010).

#### 4.7 Dermatitis herpetiformis

Dermatitis herpetiformis (DH) is a gluten-sensitive skin disease characterized by an itchy, blistering rash which diagnosis is based on the presence of granular IgA deposits in the epidermal-dermal junction observed by direct immunofluorescence. About 75-80% of patients have an associated gluten-sensitive enteropathy with villous atrophy identical to that found in CD, even if gastrointestinal symptoms are rare, and the remaining show increased amount of  $\gamma\delta$  receptor bearing T lymphocytes in the jejunal mucosa (Savilahti *et al*, 1992, Reunala, 1998). Both enteropathy and cutaneous rash recover with a gluten-free diet and relapse when diet is withdrawn (Fry *et al*, 1973, Reunala *et al*, 1977), suggesting that DH might be a cutaneous manifestation of CD. Moreover, almost all patients affected by DH carry the HLA alleles DQA1\*0501 and DQB1\*0201 typical of CD (Fronck *et al*, 1991). Since 1970, it is thought that patients with DH but without clinical sign of CD have an increased risk of developing cancer (Gjone & Nordoy, 1970), and some cases of patients with DH and lymphoma were reported (Jenkins *et al*, 1983, Reunala *et al*, 1982). The first large population-based cohort study assessing lymphoma risk in DH included 976 patients affected by DH without concomitant CD diagnosed from 1964 to 1983 in Sweden (Sigurgeirsson *et al*, 1994). The RR of developing cancer resulted 1.4 (95% CI= 1.1-1.7) in male patients and 1.2 (95% CI= 0.8-1.7) in female patients. This increased risk lost significance if lymphomas were excluded from analysis. In fact, analyzing cancer by subtype, it was found only a significant association with NHL (RR 5.4 95% CI= 2.2-11.1 in male patients and 4.5 95% CI=0.9-13.2 in female patients). The median time between the first admission to hospital and diagnosis of lymphoma was 4 years and the median age at diagnosis was 64 years. Most lymphomas were localized outside the gastrointestinal tract and were of the B cell phenotype. Only one case was classified as EATL. DH indeed is not only associated with EATL, but also with B-cell lymphomas, which may occur both within and outside the gastrointestinal tract as nodal or extranodal disease (Hervonen *et al*, 2005, Viljamaa *et al*, 2006). One possible reason for this discrepancy may be the less severe small bowel damage in DH with respect to that in CD. Occurrence of malignancy was assessed in another DH-patient cohort mainly treated with dapsone and gluten-free diet compared with patients affected by CD and general population (Collin *et al*, 1996). This study cohort included 305 consecutive Finnish patients diagnosed with DH from 1970 to 1992 and 383 patients diagnosed with CD. The only significantly increased SIR was that for NHL among patients with DH (10.3; 95% CI 2.8-26.3), while the overall incidence of other malignancies was not increased. Of four patients who developed NHL, three were adhering to a gluten-free diet, but two for less than five years, which is probably a too short period to exhibit a protective effect against malignancy (Holmes *et al*, 1989). Extension of the follow up period for a further 12 years confirmed that patients who have adhered to a strict gluten-free diet for more than 5 years have no increased risk of developing lymphoma compared to the general population (Lewis *et al*, 1996), supporting the protective role of a gluten-free diet against lymphoma development in DH (Hervonen *et al*, 2005). Moreover, three patients had abnormal small bowel villous architecture, while one patient had normal mucosa, implying that a normal small bowel mucosa in DH does not protect from lymphoma. Another retrospective cohort study has reported a 2-fold increased risk for malignant lymphoma (SIR=1.9; 95% CI 0.8-3.9) (Askling *et al*, 2002). Importantly, NHL occurrence seems to be reduced in DH patients whose diagnosis was made over the recent years (Viljamaa *et al*, 2006) maybe due to a less adherence of patients to a gluten-free diet in the past, not considered as essential as nowadays in DH. First-degree relatives of patients with DH or CD have an higher risk of

developing a gluten-sensitive enteropathy (Hervonen *et al*, 2002). This is not true for lymphoma risk, as demonstrated in a large series of patients with DH and their first-degree relatives, where three lymphoma cases (0.2%) were diagnosed among 1.825 first-degree relatives, compared with the prevalence in the general population of 0.1%. The aetiopathology of lymphoma development in patients with DH is unknown, but several mechanisms may be involved, such as the polyclonal stimulation of B or T lymphocytes by gluten in the gastrointestinal tract, leading to the transformation in a malignant clone.

## 5. Conclusions

The relationship existing between autoimmunity and cancer continues to fascinate clinicians and physicians. Many pathogenic and therapeutic overlaps have been demonstrated so far in these two intriguing and closely interrelated fields but several challenges remain open to future development. The exact pathogenic mechanism connecting both diseases remain still poorly understood and additional studies will explore genetic, biologic and inflammatory mechanisms underlying lymphoma development. Further epidemiologic studies are needed to ascertain which host factors may predispose in the setting of an autoimmune disease to develop a malignancy in general, and a lymphoproliferative disorder in particular, in order to define more accurately the pre-treatment risk. Finally, more surveillance studies will clarify if novel immunomodulatory treatments increase or decrease lymphoma risk. A more clear elucidation of these critical issues will lead to the development of novel therapeutic options able to improve the prevention and/or treatment of lymphomas in the setting of autoimmunity.

## 6. References

- Abu-Shakra, M., Guillemin, F. & Lee, P. (1993) Cancer in systemic sclerosis. *Arthritis and Rheumatism*, 36, 460-464.
- Adamson, T.C., 3rd, Fox, R.L., Frisman, D.M. & Howell, F.V. (1983) Immunohistologic analysis of lymphoid infiltrates in primary sjogren's syndrome using monoclonal antibodies. *Journal of Immunology (Baltimore, Md.: 1950)*, 130, 203-208.
- Alspaugh, M.A., Henle, G., Lennette, E.T. & Henle, W. (1981) Elevated levels of antibodies to epstein-barr virus antigens in sera and synovial fluids of patients with rheumatoid arthritis. *The Journal of Clinical Investigation*, 67, 1134-1140.
- Al-Toma, A., Verbeek, W.H., Hadithi, M., von Blomberg, B.M. & Mulder, C.J. (2007) Survival in refractory coeliac disease and enteropathy-associated T-cell lymphoma: Retrospective evaluation of single-centre experience. *Gut*, 56, 1373-1378.
- Ambinder, R.F. (2003) Epstein-barr virus-associated lymphoproliferative disorders. *Reviews in Clinical and Experimental Hematology*, 7, 362-374.
- Ambrosetti, A., Zanotti, R., Pattaro, C., Lenzi, L., Chilosi, M., Caramaschi, P., Arcaini, L., Pasini, F., Biasi, D., Orlandi, E., D'Adda, M., Lucioni, M. & Pizzolo, G. (2004) Most cases of primary salivary mucosa-associated lymphoid tissue lymphoma are associated either with sjogren syndrome or hepatitis C virus infection. *British Journal of Haematology*, 126, 43-49.
- Anaya, J.M., McGuff, H.S., Banks, P.M. & Talal, N. (1996) Clinicopathological factors relating malignant lymphoma with sjogren's syndrome. *Seminars in Arthritis and Rheumatism*, 25, 337-346.

- Anderson, L.A., Gadalla, S., Morton, L.M., Landgren, O., Pfeiffer, R., Warren, J.L., Berndt, S.I., Ricker, W., Parsons, R. & Engels, E.A. (2009) Population-based study of autoimmune conditions and the risk of specific lymphoid malignancies. *International Journal of Cancer. Journal International Du Cancer*, 125, 398-405.
- Anderson, L.G. & Talal, N. (1972) The spectrum of benign to malignant lymphoproliferation in sjogren's syndrome. *Clinical and Experimental Immunology*, 10, 199-221.
- Ansell, S.M., Grant, C.S. & Habermann, T.M. (1999) Primary thyroid lymphoma. *Seminars in Oncology*, 26, 316-323.
- Aozasa, K. (1990) Hashimoto's thyroiditis as a risk factor of thyroid lymphoma. *Acta Pathologica Japonica*, 40, 459-468.
- Aringer, M., Wintersberger, W., Steiner, C.W., Kiener, H., Presterl, E., Jaeger, U., Smolen, J.S. & Graninger, W.B. (1994) High levels of bcl-2 protein in circulating T lymphocytes, but not B lymphocytes, of patients with systemic lupus erythematosus. *Arthritis and Rheumatism*, 37, 1423-1430.
- Arnaud, L., Chryssostalis, A., Terris, B., Pavy, S., Chaussade, S., Kahan, A. & Allanore, Y. (2006) Systemic sclerosis and gastric MALT lymphoma. *Joint, Bone, Spine : Revue Du Rhumatisme*, 73, 105-108.
- Ashton-Key, M., Diss, T.C., Pan, L., Du, M.Q. & Isaacson, P.G. (1997) Molecular analysis of T-cell clonality in ulcerative jejunitis and enteropathy-associated T-cell lymphoma. *The American Journal of Pathology*, 151, 493-498.
- Askling, J., Linet, M., Gridley, G., Halstensen, T.S., Ekstrom, K. & Ekblom, A. (2002) Cancer incidence in a population-based cohort of individuals hospitalized with celiac disease or dermatitis herpetiformis. *Gastroenterology*, 123, 1428-1435.
- Askling, J., Brandt, L., Lapidus, A., Karlen, P., Bjorkholm, M., Lofberg, R. & Ekblom, A. (2005) Risk of haematopoietic cancer in patients with inflammatory bowel disease. *Gut*, 54, 617-622.
- Askling, J., van Vollenhoven, R.F., Granath, F., Raaschou, P., Fored, C.M., Baecklund, E., Dackhammar, C., Feltelius, N., Coster, L., Geborek, P., Jacobsson, L.T., Lindblad, S., Rantapaa-Dahlqvist, S., Saxne, T. & Klareskog, L. (2009) Cancer risk in patients with rheumatoid arthritis treated with anti-tumor necrosis factor alpha therapies: Does the risk change with the time since start of treatment? *Arthritis and Rheumatism*, 60, 3180-3189.
- Askling, J., Fored, C.M., Baecklund, E., Brandt, L., Backlin, C., Ekblom, A., Sundstrom, C., Bertilsson, L., Coster, L., Geborek, P., Jacobsson, L.T., Lindblad, S., Lysholm, J., Rantapaa-Dahlqvist, S., Saxne, T., Klareskog, L. & Feltelius, N. (2005) Haematopoietic malignancies in rheumatoid arthritis: Lymphoma risk and characteristics after exposure to tumour necrosis factor antagonists. *Annals of the Rheumatic Diseases*, 64, 1414-1420.
- Baecklund, E., Ekblom, A., Sparen, P., Feltelius, N. & Klareskog, L. (1998) Disease activity and risk of lymphoma in patients with rheumatoid arthritis: Nested case-control study. *BMJ (Clinical Research Ed.)*, 317, 180-181.
- Baecklund, E., Sundstrom, C., Ekblom, A., Catrina, A.I., Biberfeld, P., Feltelius, N. & Klareskog, L. (2003) Lymphoma subtypes in patients with rheumatoid arthritis: Increased proportion of diffuse large B cell lymphoma. *Arthritis and Rheumatism*, 48, 1543-1550.

- Baecklund, E., Iliadou, A., Askling, J., Ekblom, A., Backlin, C., Granath, F., Catrina, A.I., Rosenquist, R., Feltelius, N., Sundstrom, C. & Klareskog, L. (2006a) Association of chronic inflammation, not its treatment, with increased lymphoma risk in rheumatoid arthritis. *Arthritis and Rheumatism*, 54, 692-701.
- Baecklund, E., Backlin, C., Iliadou, A., Granath, F., Ekblom, A., Amini, R.M., Feltelius, N., Enblad, G., Sundstrom, C., Klareskog, L., Askling, J. & Rosenquist, R. (2006b) Characteristics of diffuse large B cell lymphomas in rheumatoid arthritis. *Arthritis and Rheumatism*, 54, 3774-3781.
- Bagdi, E., Diss, T.C., Munson, P. & Isaacson, P.G. (1999) Mucosal intra-epithelial lymphocytes in enteropathy-associated T-cell lymphoma, ulcerative jejunitis, and refractory celiac disease constitute a neoplastic population. *Blood*, 94, 260-264.
- Baker, J.A., Weiss, J.R., Czuczman, M.S., Menezes, R.J., Ambrosone, C.B. & Moysich, K.B. (2005) Regular use of aspirin or acetaminophen and risk of non-hodgkin lymphoma. *Cancer Causes & Control : CCC*, 16, 301-308.
- Baker, K.P., Edwards, B.M., Main, S.H., Choi, G.H., Wager, R.E., Halpern, W.G., Lappin, P.B., Riccobene, T., Abramian, D., Sekut, L., Sturm, B., Poortman, C., Minter, R.R., Dobson, C.L., Williams, E., Carmen, S., Smith, R., Roschke, V., Hilbert, D.M., Vaughan, T.J. & Albert, V.R. (2003) Generation and characterization of LymphoStat-B, a human monoclonal antibody that antagonizes the bioactivities of B lymphocyte stimulator. *Arthritis and Rheumatism*, 48, 3253-3265.
- Balandraud, N., Roudier, J. & Roudier, C. (2005) What are the links between epstein-barr virus, lymphoma, and tumor necrosis factor antagonism in rheumatoid arthritis? *Seminars in Arthritis and Rheumatism*, 34, 31-33.
- Balandraud, N., Meynard, J.B., Auger, I., Sovran, H., Mugnier, B., Reviron, D., Roudier, J. & Roudier, C. (2003) Epstein-barr virus load in the peripheral blood of patients with rheumatoid arthritis: Accurate quantification using real-time polymerase chain reaction. *Arthritis and Rheumatism*, 48, 1223-1228.
- Banchereau, J. & Pascual, V. (2006) Type I interferon in systemic lupus erythematosus and other autoimmune diseases. *Immunity*, 25, 383-392.
- Beauparlant, P., Papp, K. & Haraoui, B. (1999) The incidence of cancer associated with the treatment of rheumatoid arthritis. *Seminars in Arthritis and Rheumatism*, 29, 148-158.
- Beiderbeck, A.B., Holly, E.A., Sturkenboom, M.C., Coebergh, J.W., Stricker, B.H. & Leufkens, H.G. (2003) No increased risk of non-hodgkin's lymphoma with steroids, estrogens and psychotropics (netherlands). *Cancer Causes & Control : CCC*, 14, 639-644.
- Berek, C. & Kim, H.J. (1997) B-cell activation and development within chronically inflamed synovium in rheumatoid and reactive arthritis. *Seminars in Immunology*, 9, 261-268.
- Bernatsky, S., Lee, J.L. & Rahme, E. (2007) Non-hodgkin's lymphoma--meta-analyses of the effects of corticosteroids and non-steroidal anti-inflammatories. *Rheumatology (Oxford, England)*, 46, 690-694.
- Bernatsky, S., Clarke, A. & Ramsey-Goldman, R. (2002) Malignancy and systemic lupus erythematosus. *Current Rheumatology Reports*, 4, 351-358.
- Bernatsky, S., Ramsey-Goldman, R., Isenberg, D., Rahman, A., Dooley, M.A., Sibley, J., Boivin, J.F., Joseph, L., Armitage, J., Zoma, A. & Clarke, A. (2007) Hodgkin's lymphoma in systemic lupus erythematosus. *Rheumatology (Oxford, England)*, 46, 830-832.

- Bernatsky, S., Joseph, L., Boivin, J.F., Gordon, C., Urowitz, M., Gladman, D., Fortin, P.R., Ginzler, E., Bae, S.C., Barr, S., Edworthy, S., Isenberg, D., Rahman, A., Petri, M., Alarcon, G.S., Aranow, C., Dooley, M.A., Rajan, R., Senecal, J.L., Zummer, M., Manzi, S., Ramsey-Goldman, R. & Clarke, A.E. (2008) The relationship between cancer and medication exposures in systemic lupus erythematosis: A case-cohort study. *Annals of the Rheumatic Diseases*, 67, 74-79.
- Bernatsky, S., Ramsey-Goldman, R., Rajan, R., Boivin, J.F., Joseph, L., Lachance, S., Cournoyer, D., Zoma, A., Manzi, S., Ginzler, E., Urowitz, M., Gladman, D., Fortin, P.R., Edworthy, S., Barr, S., Gordon, C., Bae, S.C., Sibley, J., Steinsson, K., Nived, O., Sturfelt, G., St Pierre, Y. & Clarke, A. (2005a) Non-hodgkin's lymphoma in systemic lupus erythematosis. *Annals of the Rheumatic Diseases*, 64, 1507-1509.
- Bernatsky, S., Boivin, J.F., Joseph, L., Rajan, R., Zoma, A., Manzi, S., Ginzler, E., Urowitz, M., Gladman, D., Fortin, P.R., Petri, M., Edworthy, S., Barr, S., Gordon, C., Bae, S.C., Sibley, J., Isenberg, D., Rahman, A., Aranow, C., Dooley, M.A., Steinsson, K., Nived, O., Sturfelt, G., Alarcon, G., Senecal, J.L., Zummer, M., Hanly, J., Ensworth, S., Pope, J., El-Gabalawy, H., McCarthy, T., St Pierre, Y., Ramsey-Goldman, R. & Clarke, A. (2005b) An international cohort study of cancer in systemic lupus erythematosis. *Arthritis and Rheumatism*, 52, 1481-1490.
- Bernstein, L. & Ross, R.K. (1992) Prior medication use and health history as risk factors for non-hodgkin's lymphoma: Preliminary results from a case-control study in los angeles county. *Cancer Research*, 52, 5510s-5515s.
- Bishton, M.J. & Haynes, A.P. (2007) Combination chemotherapy followed by autologous stem cell transplant for enteropathy-associated T cell lymphoma. *British Journal of Haematology*, 136, 111-113.
- Boffetta, P., Gridley, G. & Lindelof, B. (2001) Cancer risk in a population-based cohort of patients hospitalized for psoriasis in sweden. *The Journal of Investigative Dermatology*, 117, 1531-1537.
- Bologna, C., Picot, M.C., Jorgensen, C., Viu, P., Verdier, R. & Sany, J. (1997) Study of eight cases of cancer in 426 rheumatoid arthritis patients treated with methotrexate. *Annals of the Rheumatic Diseases*, 56, 97-102.
- Bombardieri, M., Barone, F., Humby, F., Kelly, S., McGurk, M., Morgan, P., Challacombe, S., De Vita, S., Valesini, G., Spencer, J. & Pitzalis, C. (2007) Activation-induced cytidine deaminase expression in follicular dendritic cell networks and interfollicular large B cells supports functionality of ectopic lymphoid neogenesis in autoimmune sialoadenitis and MALT lymphoma in sjogren's syndrome. *Journal of Immunology (Baltimore, Md.: 1950)*, 179, 4929-4938.
- Bongartz, T., Warren, F.C., Mines, D., Matteson, E.L., Abrams, K.R. & Sutton, A.J. (2009) Etanercept therapy in rheumatoid arthritis and the risk of malignancies: A systematic review and individual patient data meta-analysis of randomised controlled trials. *Annals of the Rheumatic Diseases*, 68, 1177-1183.
- Bongartz, T., Sutton, A.J., Sweeting, M.J., Buchan, I., Matteson, E.L. & Montori, V. (2006) Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: Systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *JAMA : The Journal of the American Medical Association*, 295, 2275-2285.

- Brandtzaeg, P. & Johansen, F.E. (2005) Mucosal B cells: Phenotypic characteristics, transcriptional regulation, and homing properties. *Immunological Reviews*, 206, 32-63.
- Brito-Zeron, P., Ramos-Casals, M., Bove, A., Sentis, J. & Font, J. (2007) Predicting adverse outcomes in primary sjogren's syndrome: Identification of prognostic factors. *Rheumatology (Oxford, England)*, 46, 1359-1362.
- Brown, S.L., Greene, M.H., Gershon, S.K., Edwards, E.T. & Braun, M.M. (2002) Tumor necrosis factor antagonist therapy and lymphoma development: Twenty-six cases reported to the food and drug administration. *Arthritis and Rheumatism*, 46, 3151-3158.
- Burke, J.S. (1999) Are there site-specific differences among the MALT lymphomas--morphologic, clinical? *American Journal of Clinical Pathology*, 111, S133-43.
- Caponi, L., Anzilotti, C., Longombardo, G. & Migliorini, P. (2007) Antibodies directed against ribosomal P proteins cross-react with phospholipids. *Clinical and Experimental Immunology*, 150, 140-143.
- Cartwright, R.A., McKinney, P.A., O'Brien, C., Richards, I.D., Roberts, B., Lauder, I., Darwin, C.M., Bernard, S.M. & Bird, C.C. (1988) Non-hodgkin's lymphoma: Case control epidemiological study in yorkshire. *Leukemia Research*, 12, 81-88.
- Catassi, C., Fabiani, E., Corrao, G., Barbato, M., De Renzo, A., Carella, A.M., Gabrielli, A., Leoni, P., Carroccio, A., Baldassarre, M., Bertolani, P., Caramaschi, P., Sozzi, M., Guariso, G., Volta, U., Corazza, G.R. & Italian Working Group on Coeliac Disease and Non-Hodgkin's-Lymphoma. (2002) Risk of non-hodgkin lymphoma in celiac disease. *JAMA : The Journal of the American Medical Association*, 287, 1413-1419.
- Cellier, C., Delabesse, E., Helmer, C., Patey, N., Matuchansky, C., Jabri, B., Macintyre, E., Cerf-Bensussan, N. & Brousse, N. (2000) Refractory sprue, coeliac disease, and enteropathy-associated T-cell lymphoma. french coeliac disease study group. *Lancet*, 356, 203-208.
- Cellier, C., Patey, N., Mauvieux, L., Jabri, B., Delabesse, E., Cervoni, J.P., Burtin, M.L., Guy-Grand, D., Bouhnik, Y., Modigliani, R., Barbier, J.P., Macintyre, E., Brousse, N. & Cerf-Bensussan, N. (1998) Abnormal intestinal intraepithelial lymphocytes in refractory sprue. *Gastroenterology*, 114, 471-481.
- Cerhan, J.R., Anderson, K.E., Janney, C.A., Vachon, C.M., Witzig, T.E. & Habermann, T.M. (2003) Association of aspirin and other non-steroidal anti-inflammatory drug use with incidence of non-hodgkin lymphoma. *International Journal of Cancer. Journal International Du Cancer*, 106, 784-788.
- Chang, E.T., Smedby, K.E., Hjalgrim, H., Schollkopf, C., Porwit-MacDonald, A., Sundstrom, C., Tani, E., d'Amore, F., Melbye, M., Adami, H.O. & Glimelius, B. (2005) Medication use and risk of non-hodgkin's lymphoma. *American Journal of Epidemiology*, 162, 965-974.
- Chatterjee, S., Dombi, G.W., Severson, R.K. & Mayes, M.D. (2005) Risk of malignancy in scleroderma: A population-based cohort study. *Arthritis and Rheumatism*, 52, 2415-2424.
- Chott, A., Dragosics, B. & Radaszkiewicz, T. (1992) Peripheral T-cell lymphomas of the intestine. *The American Journal of Pathology*, 141, 1361-1371.
- Chott, A., Haedicke, W., Mosberger, I., Fodinger, M., Winkler, K., Mannhalter, C. & Muller-Hermelink, H.K. (1998) Most CD56+ intestinal lymphomas are CD8+CD5-T-cell



- lymphomas of monomorphic small to medium size histology. *The American Journal of Pathology*, 153, 1483-1490.
- Choubey, D. & Panchanathan, R. (2008) Interferon-inducible Ifi200-family genes in systemic lupus erythematosus. *Immunology Letters*, 119, 32-41.
- Choubey, D. & Kotzin, B.L. (2002) Interferon-inducible p202 in the susceptibility to systemic lupus. *Frontiers in Bioscience : A Journal and Virtual Library*, 7, e252-62.
- Choubey, D., Deka, R. & Ho, S.M. (2008) Interferon-inducible IFI16 protein in human cancers and autoimmune diseases. *Frontiers in Bioscience : A Journal and Virtual Library*, 13, 598-608.
- Collin, P., Pukkala, E. & Reunala, T. (1996) Malignancy and survival in dermatitis herpetiformis: A comparison with coeliac disease. *Gut*, 38, 528-530.
- Collin, P., Reunala, T., Pukkala, E., Laippala, P., Keyrilainen, O. & Pasternack, A. (1994) Coeliac disease--associated disorders and survival. *Gut*, 35, 1215-1218.
- Corrao, G., Corazza, G.R., Bagnardi, V., Brusco, G., Ciacci, C., Cottone, M., Sategna Guidetti, C., Usai, P., Cesari, P., Pelli, M.A., Loperfido, S., Volta, U., Calabro, A., Certo, M. & Club del Tenue Study Group. (2001) Mortality in patients with coeliac disease and their relatives: A cohort study. *Lancet*, 358, 356-361.
- Costenbader, K.H., Glass, R., Cui, J. & Shadick, N. (2006) Risk of serious infections and malignancies with anti-TNF antibody therapy in rheumatoid arthritis. *JAMA : The Journal of the American Medical Association*, 296, 2201; author reply 2203-4.
- d'Amore, F., Brincker, H., Gronbaek, K., Thorling, K., Pedersen, M., Jensen, M.K., Andersen, E., Pedersen, N.T. & Mortensen, L.S. (1994) Non-hodgkin's lymphoma of the gastrointestinal tract: A population-based analysis of incidence, geographic distribution, clinicopathologic presentation features, and prognosis. danish lymphoma study group. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology*, 12, 1673-1684.
- Daniels, T.E. (1984) Labial salivary gland biopsy in sjogren's syndrome. assessment as a diagnostic criterion in 362 suspected cases. *Arthritis and Rheumatism*, 27, 147-156.
- Daum, S., Cellier, C. & Mulder, C.J. (2005) Refractory coeliac disease. *Best Practice & Research. Clinical Gastroenterology*, 19, 413-424.
- Daum, S., Ullrich, R., Heise, W., Dederke, B., Foss, H.D., Stein, H., Thiel, E., Zeitz, M. & Riecken, E.O. (2003) Intestinal non-hodgkin's lymphoma: A multicenter prospective clinical study from the german study group on intestinal non-hodgkin's lymphoma. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology*, 21, 2740-2746.
- Daum, S., Weiss, D., Hummel, M., Ullrich, R., Heise, W., Stein, H., Riecken, E.O., Foss, H.D. & Intestinal Lymphoma Study Group. (2001) Frequency of clonal intraepithelial T lymphocyte proliferations in enteropathy-type intestinal T cell lymphoma, coeliac disease, and refractory sprue. *Gut*, 49, 804-812.
- Dayan, C.M. & Daniels, G.H. (1996) Chronic autoimmune thyroiditis. *The New England Journal of Medicine*, 335, 99-107.
- Derk, C.T., Conway, R.T. & Jimenez, S.A. (2004) Primary B-cell lymphoma of the tongue in a patient with systemic sclerosis. *Oral Oncology*, 40, 103-106.
- Derk, C.T., Rasheed, M., Artlett, C.M. & Jimenez, S.A. (2006) A cohort study of cancer incidence in systemic sclerosis. *The Journal of Rheumatology*, 33, 1113-1116.

- Derringer, G.A., Thompson, L.D., Frommelt, R.A., Bijwaard, K.E., Heffess, C.S. & Abbondanzo, S.L. (2000) Malignant lymphoma of the thyroid gland: A clinicopathologic study of 108 cases. *The American Journal of Surgical Pathology*, 24, 623-639.
- Di Cristofano, A., Kotsi, P., Peng, Y.F., Cordon-Cardo, C., Elkon, K.B. & Pandolfi, P.P. (1999) Impaired fas response and autoimmunity in pten<sup>+/-</sup> mice. *Science (New York, N.Y.)*, 285, 2122-2125.
- Di Sabatino, A. & Corazza, G.R. (2009) Coeliac disease. *Lancet*, 373, 1480-1493.
- Do, R.K. & Chen-Kiang, S. (2002) Mechanism of BLYS action in B cell immunity. *Cytokine & Growth Factor Reviews*, 13, 19-25.
- Domizio, P., Owen, R.A., Shepherd, N.A., Talbot, I.C. & Norton, A.J. (1993) Primary lymphoma of the small intestine. A clinicopathological study of 119 cases. *The American Journal of Surgical Pathology*, 17, 429-442.
- Du, M.Q., Xu, C.F., Diss, T.C., Peng, H.Z., Wotherspoon, A.C., Isaacson, P.G. & Pan, L.X. (1996) Intestinal dissemination of gastric mucosa-associated lymphoid tissue lymphoma. *Blood*, 88, 4445-4451.
- Duggal, L., Gupta, S., Aggarwal, P.K., Sachar, V.P. & Bhalla, S. (2002) Hodgkin's disease and scleroderma. *The Journal of the Association of Physicians of India*, 50, 1186-1188.
- Duncan, S.C. & Winkelmann, R.K. (1979) Cancer and scleroderma. *Archives of Dermatology*, 115, 950-955.
- Edinger, J.W., Bonneville, M., Scotet, E., Houssaint, E., Schumacher, H.R. & Posnett, D.N. (1999) EBV gene expression not altered in rheumatoid synovia despite the presence of EBV antigen-specific T cell clones. *Journal of Immunology (Baltimore, Md.: 1950)*, 162, 3694-3701.
- Eguchi, K. (2001) Apoptosis in autoimmune diseases. *Internal Medicine (Tokyo, Japan)*, 40, 275-284.
- Ekstrom Smedby, K., Vajdic, C.M., Falster, M., Engels, E.A., Martinez-Maza, O., Turner, J., Hjalgrim, H., Vineis, P., Seniori Costantini, A., Bracci, P.M., Holly, E.A., Willett, E., Spinelli, J.J., La Vecchia, C., Zheng, T., Becker, N., De Sanjose, S., Chiu, B.C., Dal Maso, L., Cocco, P., Maynadie, M., Foretova, L., Staines, A., Brennan, P., Davis, S., Severson, R., Cerhan, J.R., Breen, E.C., Birmann, B., Grulich, A.E. & Cozen, W. (2008) Autoimmune disorders and risk of non-hodgkin lymphoma subtypes: A pooled analysis within the InterLymph consortium. *Blood*, 111, 4029-4038.
- Ekstrom, K., Hjalgrim, H., Brandt, L., Baecklund, E., Klareskog, L., Ekbom, A. & Askling, J. (2003) Risk of malignant lymphomas in patients with rheumatoid arthritis and in their first-degree relatives. *Arthritis and Rheumatism*, 48, 963-970.
- El Fassi, D., Clemmensen, O., Nielsen, C.H., Silkiss, R.Z. & Hegedus, L. (2007a) Evidence of intrathyroidal B-lymphocyte depletion after rituximab therapy in a patient with graves' disease. *The Journal of Clinical Endocrinology and Metabolism*, 92, 3762-3763.
- El Fassi, D., Nielsen, C.H., Bonnema, S.J., Hasselbalch, H.C. & Hegedus, L. (2007b) B lymphocyte depletion with the monoclonal antibody rituximab in graves' disease: A controlled pilot study. *The Journal of Clinical Endocrinology and Metabolism*, 92, 1769-1772.
- Elfstrom, P., Granath, F., Ekstrom Smedby, K., Montgomery, S.M., Askling, J., Ekbom, A. & Ludvigsson, J.F. (2011) Risk of lymphoproliferative malignancy in relation to small intestinal histopathology among patients with celiac disease. *Journal of the National Cancer Institute*, 103, 436-444.

- Ellman, M.H., Hurwitz, H., Thomas, C. & Kozloff, M. (1991) Lymphoma developing in a patient with rheumatoid arthritis taking low dose weekly methotrexate. *The Journal of Rheumatology*, 18, 1741-1743.
- Engels, E.A., Cerhan, J.R., Linet, M.S., Cozen, W., Colt, J.S., Davis, S., Gridley, G., Severson, R.K. & Hartge, P. (2005) Immune-related conditions and immune-modulating medications as risk factors for non-hodgkin's lymphoma: A case-control study. *American Journal of Epidemiology*, 162, 1153-1161.
- Farstad, I.N., Johansen, F.E., Vlatkovic, L., Jahnsen, J., Scott, H., Fausa, O., Bjorneklett, A., Brandtzaeg, P. & Halstensen, T.S. (2002) Heterogeneity of intraepithelial lymphocytes in refractory sprue: Potential implications of CD30 expression. *Gut*, 51, 372-378.
- Feng, W.H., Cohen, J.L., Fischer, S., Li, L., Sneller, M., Goldbach-Mansky, R., Raab-Traub, N., Delecluse, H.J. & Kenney, S.C. (2004) Reactivation of latent epstein-barr virus by methotrexate: A potential contributor to methotrexate-associated lymphomas. *Journal of the National Cancer Institute*, 96, 1691-1702.
- Franklin, J., Lunt, M., Bunn, D., Symmons, D. & Silman, A. (2006) Incidence of lymphoma in a large primary care derived cohort of cases of inflammatory polyarthritis. *Annals of the Rheumatic Diseases*, 65, 617-622.
- Franklin, J.P., Symmons, D.P. & Silman, A.J. (2005) Risk of lymphoma in patients with RA treated with anti-TNFalpha agents. *Annals of the Rheumatic Diseases*, 64, 657-658.
- Freimark, B., Fantozzi, R., Bone, R., Bordin, G. & Fox, R. (1989) Detection of clonally expanded salivary gland lymphocytes in sjogren's syndrome. *Arthritis and Rheumatism*, 32, 859-869.
- Friedman, D.F., Cho, E.A., Goldman, J., Carmack, C.E., Besa, E.C., Hardy, R.R. & Silberstein, L.E. (1991) The role of clonal selection in the pathogenesis of an autoreactive human B cell lymphoma. *The Journal of Experimental Medicine*, 174, 525-537.
- Fronek, Z., Cheung, M.M., Hanbury, A.M. & Kagnoff, M.F. (1991) Molecular analysis of HLA DP and DQ genes associated with dermatitis herpetiformis. *The Journal of Investigative Dermatology*, 97, 799-802.
- Fry, L., Seah, P.P., Riches, D.J. & Hoffbrand, A.V. (1973) Clearance of skin lesions in dermatitis herpetiformis after gluten withdrawal. *Lancet*, 1, 288-291.
- Gale, J., Simmonds, P.D., Mead, G.M., Sweetenham, J.W. & Wright, D.H. (2000) Enteropathy-type intestinal T-cell lymphoma: Clinical features and treatment of 31 patients in a single center. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology*, 18, 795-803.
- Gallamini, A., Zaja, F., Patti, C., Billio, A., Specchia, M.R., Tucci, A., Levis, A., Manna, A., Secondo, V., Rigacci, L., Pinto, A., Iannitto, E., Zoli, V., Torchio, P., Pileri, S. & Tarella, C. (2007) Alemtuzumab (campath-1H) and CHOP chemotherapy as first-line treatment of peripheral T-cell lymphoma: Results of a GITIL (gruppo italiano terapie innovative nei linfomi) prospective multicenter trial. *Blood*, 110, 2316-2323.
- Gasparotto, D., De Vita, S., De Re, V., Marzotto, A., De Marchi, G., Scott, C.A., Gloghini, A., Ferraccioli, G. & Boiocchi, M. (2003) Extrasalivary lymphoma development in sjogren's syndrome: Clonal evolution from parotid gland lymphoproliferation and role of local triggering. *Arthritis and Rheumatism*, 48, 3181-3186.
- Geborek, P., Crnkic, M., Pettersson, I.F., Saxne, T. & South Swedish Arthritis Treatment Group. (2002) Etanercept, infliximab, and leflunomide in established rheumatoid

- arthritis: Clinical experience using a structured follow up programme in southern sweden. *Annals of the Rheumatic Diseases*, 61, 793-798.
- Geborek, P., Bladstrom, A., Turesson, C., Gulfe, A., Petersson, I.F., Saxne, T., Olsson, H. & Jacobsson, L.T. (2005) Tumour necrosis factor blockers do not increase overall tumour risk in patients with rheumatoid arthritis, but may be associated with an increased risk of lymphomas. *Annals of the Rheumatic Diseases*, 64, 699-703.
- Gelfand, J.M., Shin, D.B., Neimann, A.L., Wang, X., Margolis, D.J. & Troxel, A.B. (2006) The risk of lymphoma in patients with psoriasis. *The Journal of Investigative Dermatology*, 126, 2194-2201.
- Gellrich, S., Rutz, S., Borkowski, A., Golembowski, S., Gromnica-Ihle, E., Sterry, W. & Jahn, S. (1999) Analysis of V(H)-D-J(H) gene transcripts in B cells infiltrating the salivary glands and lymph node tissues of patients with sjogren's syndrome. *Arthritis and Rheumatism*, 42, 240-247.
- Gjone, E. & Nordoy, A. (1970) Dermatitis herpetiformis, steatorrhoea, and malignancy. *British Medical Journal*, 1, 610.
- Goodnow, C.C. (2007) Multistep pathogenesis of autoimmune disease. *Cell*, 130, 25-35.
- Grady, W.M. (2005) Transforming growth factor-beta, smads, and cancer. *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research*, 11, 3151-3154.
- Graff-Baker, A., Sosa, J.A. & Roman, S.A. (2010) Primary thyroid lymphoma: A review of recent developments in diagnosis and histology-driven treatment. *Current Opinion in Oncology*, 22, 17-22.
- Gridley, G., Klippel, J.H., Hoover, R.N. & Fraumeni, J.F., Jr. (1994) Incidence of cancer among men with the felty syndrome. *Annals of Internal Medicine*, 120, 35-39.
- Gridley, G., McLaughlin, J.K., Ekblom, A., Klareskog, L., Adami, H.O., Hacker, D.G., Hoover, R. & Fraumeni, J.F., Jr. (1993) Incidence of cancer among patients with rheumatoid arthritis. *Journal of the National Cancer Institute*, 85, 307-311.
- Halfdanarson, T.R., Rubio-Tapia, A., Ristow, K.M., Habermann, T.M., Murray, J.A. & Inwards, D.J. (2010) Patients with celiac disease and B-cell lymphoma have a better prognosis than those with T-cell lymphoma. *Clinical Gastroenterology and Hepatology: The Official Clinical Practice Journal of the American Gastroenterological Association*, 8, 1042-1047.
- Hall, S.W., Gillespie, J.J. & Tenczynski, T.F. (1978) Generalized lipodystrophy, scleroderma, and hodgkin's disease. *Archives of Internal Medicine*, 138, 1303-1304.
- Harris, N.L. (1999) Lymphoid proliferations of the salivary glands. *American Journal of Clinical Pathology*, 111, S94-103.
- Haviv, Y.S., Ben-Yehuda, A., Polliack, A. & Safadi, R. (1997) Lymphoma and systemic sclerosis--an uncommon association or possible coincidence of two disorders with a fatal outcome. *European Journal of Haematology*, 59, 194-196.
- Hellgren, K., Smedby, K.E., Feltelius, N., Baecklund, E. & Askling, J. (2010a) Do rheumatoid arthritis and lymphoma share risk factors?: A comparison of lymphoma and cancer risks before and after diagnosis of rheumatoid arthritis. *Arthritis and Rheumatism*, 62, 1252-1258.
- Hellgren, K., Iliadou, A., Rosenquist, R., Feltelius, N., Backlin, C., Enblad, G., Askling, J. & Baecklund, E. (2010b) Rheumatoid arthritis, treatment with corticosteroids and risk of malignant lymphomas: Results from a case-control study. *Annals of the Rheumatic Diseases*, 69, 654-659.

- Hervonen, K., Vornanen, M., Kautiainen, H., Collin, P. & Reunala, T. (2005) Lymphoma in patients with dermatitis herpetiformis and their first-degree relatives. *The British Journal of Dermatology*, 152, 82-86.
- Hervonen, K., Hakanen, M., Kaukinen, K., Collin, P. & Reunala, T. (2002) First-degree relatives are frequently affected in coeliac disease and dermatitis herpetiformis. *Scandinavian Journal of Gastroenterology*, 37, 51-55.
- Hill, C.L., Nguyen, A.M., Roder, D. & Roberts-Thomson, P. (2003) Risk of cancer in patients with scleroderma: A population based cohort study. *Annals of the Rheumatic Diseases*, 62, 728-731.
- Hjelmstrom, P. (2001) Lymphoid neogenesis: De novo formation of lymphoid tissue in chronic inflammation through expression of homing chemokines. *Journal of Leukocyte Biology*, 69, 331-339.
- Holly, E.A., Lele, C., Bracci, P.M. & McGrath, M.S. (1999) Case-control study of non-hodgkin's lymphoma among women and heterosexual men in the san francisco bay area, california. *American Journal of Epidemiology*, 150, 375-389.
- Holm, L.E., Blomgren, H. & Lowhagen, T. (1985) Cancer risks in patients with chronic lymphocytic thyroiditis. *The New England Journal of Medicine*, 312, 601-604.
- Holmes, G.K., Prior, P., Lane, M.R., Pope, D. & Allan, R.N. (1989) Malignancy in coeliac disease--effect of a gluten free diet. *Gut*, 30, 333-338.
- Horikawa, M., Hasegawa, M., Komura, K., Hayakawa, I., Yanaba, K., Matsushita, T., Takehara, K. & Sato, S. (2005) Abnormal natural killer cell function in systemic sclerosis: Altered cytokine production and defective killing activity. *The Journal of Investigative Dermatology*, 125, 731-737.
- Hoshida, Y., Tomita, Y., Zhiming, D., Yamauchi, A., Nakatsuka, S., Kurasono, Y., Arima, Y., Tsudo, M., Shintaku, M. & Aozasa, K. (2004) Lymphoproliferative disorders in autoimmune diseases in japan: Analysis of clinicopathological features and epstein-barr virus infection. *International Journal of Cancer. Journal International Du Cancer*, 108, 443-449.
- Hoshida, Y., Xu, J.X., Fujita, S., Nakamichi, I., Ikeda, J., Tomita, Y., Nakatsuka, S., Tamaru, J., Iizuka, A., Takeuchi, T. & Aozasa, K. (2007) Lymphoproliferative disorders in rheumatoid arthritis: Clinicopathological analysis of 76 cases in relation to methotrexate medication. *The Journal of Rheumatology*, 34, 322-331.
- Hyjek, E. & Isaacson, P.G. (1988) Primary B cell lymphoma of the thyroid and its relationship to hashimoto's thyroiditis. *Human Pathology*, 19, 1315-1326.
- Illes, A., Varoczy, L., Papp, G., Wilson, P.C., Alex, P., Jonsson, R., Kovacs, T., Konttinen, Y.T., Zeher, M., Nakken, B. & Szodoray, P. (2009) Aspects of B-cell non-hodgkin's lymphoma development: A transition from immune-reactivity to malignancy. *Scandinavian Journal of Immunology*, 69, 387-400.
- Ilyas, M., Niedobitek, G., Agathangelou, A., Barry, R.E., Read, A.E., Tierney, R., Young, L.S. & Rooney, N. (1995) Non-hodgkin's lymphoma, coeliac disease, and epstein-barr virus: A study of 13 cases of enteropathy-associated T- and B-cell lymphoma. *The Journal of Pathology*, 177, 115-122.
- Ioannidis, J.P., Vassiliou, V.A. & Moutsopoulos, H.M. (2002) Long-term risk of mortality and lymphoproliferative disease and predictive classification of primary sjogren's syndrome. *Arthritis and Rheumatism*, 46, 741-747.

- Isaacson, P.G. (1997) Lymphoma of the thyroid gland. *Current Topics in Pathology. Ergebnisse Der Pathologie*, 91, 1-14.
- Jackson, C.E. & Puck, J.M. (1999) Autoimmune lymphoproliferative syndrome, a disorder of apoptosis. *Current Opinion in Pediatrics*, 11, 521-527.
- Jacobi, A.M., Hansen, A., Kaufmann, O., Pruss, A., Burmester, G.R., Lipsky, P.E. & Dörner, T. (2002) Analysis of immunoglobulin light chain rearrangements in the salivary gland and blood of a patient with sjogren's syndrome. *Arthritis Research*, 4, R4.
- James, J.A., Kaufman, K.M., Farris, A.D., Taylor-Albert, E., Lehman, T.J. & Harley, J.B. (1997) An increased prevalence of epstein-barr virus infection in young patients suggests a possible etiology for systemic lupus erythematosus. *The Journal of Clinical Investigation*, 100, 3019-3026.
- Jenkins, D., Lynde, C.W. & Stewart, W.D. (1983) Histiocytic lymphoma occurring in a patient with dermatitis herpetiformis. *Journal of the American Academy of Dermatology*, 9, 252-256.
- Jonsson, R., Gordon, T.P. & Kontinen, Y.T. (2003) Recent advances in understanding molecular mechanisms in the pathogenesis and antibody profile of sjogren's syndrome. *Current Rheumatology Reports*, 5, 311-316.
- Kabel, P.J., Voorbij, H.A., de Haan-Meulman, M., Pals, S.T. & Drexhage, H.A. (1989) High endothelial venules present in lymphoid cell accumulations in thyroids affected by autoimmune disease: A study in men and BB rats of functional activity and development. *The Journal of Clinical Endocrinology and Metabolism*, 68, 744-751.
- Kahara, T., Iwaki, N., Kaya, H., Kurokawa, T., Yoshida, T., Ishikura, K. & Usuda, R. (2011) Transition of thyroid autoantibodies by rituximab treatment for thyroid MALT lymphoma. *Endocrine Journal*, 58, 7-12.
- Kamel, O.W., van de Rijn, M., Weiss, L.M., Del Zoppo, G.J., Hench, P.K., Robbins, B.A., Montgomery, P.G., Warnke, R.A. & Dorfman, R.F. (1993) Brief report: Reversible lymphomas associated with epstein-barr virus occurring during methotrexate therapy for rheumatoid arthritis and dermatomyositis. *The New England Journal of Medicine*, 328, 1317-1321.
- Kassan, S.S. & Moutsopoulos, H.M. (2004) Clinical manifestations and early diagnosis of sjogren syndrome. *Archives of Internal Medicine*, 164, 1275-1284.
- Kassan, S.S., Thomas, T.L., Moutsopoulos, H.M., Hoover, R., Kimberly, R.P., Budman, D.R., Costa, J., Decker, J.L. & Chused, T.M. (1978) Increased risk of lymphoma in sicca syndrome. *Annals of Internal Medicine*, 89, 888-892.
- Kato, I., Koenig, K.L., Shore, R.E., Baptiste, M.S., Lillquist, P.P., Frizzera, G., Burke, J.S. & Watanabe, H. (2002) Use of anti-inflammatory and non-narcotic analgesic drugs and risk of non-hodgkin's lymphoma (NHL) (united states). *Cancer Causes & Control : CCC*, 13, 965-974.
- Kauppi, M., Pukkala, E. & Isomaki, H. (1997) Elevated incidence of hematologic malignancies in patients with sjogren's syndrome compared with patients with rheumatoid arthritis (finland). *Cancer Causes & Control : CCC*, 8, 201-204.
- Kedar, A., Khan, A.B., Mattern, J.Q., Fisher, J., Thomas, P.R. & Freeman, A.I. (1979) Autoimmune disorders complicating adolescent hodgkin's disease. *Cancer*, 44, 112-116.
- Kim, H.J., Krenn, V., Steinhauser, G. & Berek, C. (1999) Plasma cell development in synovial germinal centers in patients with rheumatoid and reactive arthritis. *Journal of Immunology (Baltimore, Md.: 1950)*, 162, 3053-3062.

- King, J.K. & Costenbader, K.H. (2007) Characteristics of patients with systemic lupus erythematosus (SLE) and non-hodgkin's lymphoma (NHL). *Clinical Rheumatology*, 26, 1491-1494.
- Kingsmore, S.F., Hall, B.D., Allen, N.B., Rice, J.R. & Caldwell, D.S. (1992) Association of methotrexate, rheumatoid arthritis and lymphoma: Report of 2 cases and literature review. *The Journal of Rheumatology*, 19, 1462-1465.
- Kiss, E., Kovacs, L. & Szodoray, P. (2010) Malignancies in systemic lupus erythematosus. *Autoimmunity Reviews*, 9, 195-199.
- Klyachkin, M.L., Schwartz, R.W., Cibull, M., Munn, R.K., Regine, W.F., Kenady, D.E., McGrath, P.C. & Sloan, D.A. (1998) Thyroid lymphoma: Is there a role for surgery? *The American Surgeon*, 64, 234-238.
- Knecht, H., Saremaslani, P. & Hedinger, C. (1981) Immunohistological findings in hashimoto's thyroiditis, focal lymphocytic thyroiditis and thyroiditis de quervain. comparative study. *Virchows Archiv.A, Pathological Anatomy and Histology*, 393, 215-231.
- Kojima, M., Itoh, H., Shimizu, K., Saruki, N., Murayama, K., Higuchi, K., Tamaki, Y., Matsumoto, M., Hirabayashi, K., Igarishi, S., Masawa, N. & Nakamura, S. (2006) Malignant lymphoma in patients with systemic rheumatic disease (rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, and dermatomyositis): A clinicopathologic study of 24 japanese cases. *International Journal of Surgical Pathology*, 14, 43-48.
- Kratz, A., Campos-Neto, A., Hanson, M.S. & Ruddle, N.H. (1996) Chronic inflammation caused by lymphotoxin is lymphoid neogenesis. *The Journal of Experimental Medicine*, 183, 1461-1472.
- Kremer, J.M. (1997) Is methotrexate oncogenic in patients with rheumatoid arthritis? *Seminars in Arthritis and Rheumatism*, 26, 785-787.
- Laabi, Y. & Strasser, A. (2000) Immunology. lymphocyte survival--ignorance is BLys. *Science (New York, N.Y.)*, 289, 883-884.
- Laing, R.W., Hoskin, P., Hudson, B.V., Hudson, G.V., Harmer, C., Bennett, M.H. & MacLennan, K.A. (1994) The significance of MALT histology in thyroid lymphoma: A review of patients from the BNLI and royal marsden hospital. *Clinical Oncology (Royal College of Radiologists (Great Britain))*, 6, 300-304.
- Landgren, O., Engels, E.A., Pfeiffer, R.M., Gridley, G., Mellemkjaer, L., Olsen, J.H., Kerstann, K.F., Wheeler, W., Hemminki, K., Linet, M.S. & Goldin, L.R. (2006) Autoimmunity and susceptibility to hodgkin lymphoma: A population-based case-control study in scandinavia. *Journal of the National Cancer Institute*, 98, 1321-1330.
- Legler, D.F., Loetscher, M., Roos, R.S., Clark-Lewis, I., Baggiolini, M. & Moser, B. (1998) B cell-attracting chemokine 1, a human CXC chemokine expressed in lymphoid tissues, selectively attracts B lymphocytes via BLR1/CXCR5. *The Journal of Experimental Medicine*, 187, 655-660.
- Leombruno, J.P., Einarson, T.R. & Keystone, E.C. (2009) The safety of anti-tumour necrosis factor treatments in rheumatoid arthritis: Meta and exposure-adjusted pooled analyses of serious adverse events. *Annals of the Rheumatic Diseases*, 68, 1136-1145.
- Leprince, C., Cohen-Kaminsky, S., Berrih-Aknin, S., Vernet-Der Garabedian, B., Treton, D., Galanaud, P. & Richard, Y. (1990) Thymic B cells from myasthenia gravis patients are activated B cells. phenotypic and functional analysis. *Journal of Immunology (Baltimore, Md.: 1950)*, 145, 2115-2122.

- Lewis, H.M., Renaula, T.L., Garioch, J.J., Leonard, J.N., Fry, J.S., Collin, P., Evans, D. & Fry, L. (1996) Protective effect of gluten-free diet against development of lymphoma in dermatitis herpetiformis. *The British Journal of Dermatology*, 135, 363-367.
- Liote, F., Pertuiset, E., Cochand-Priollet, B., D'Agay, M.F., Dombret, H., Numeric, P., D'Anglejan, G. & Kuntz, D. (1995) Methotrexate related B lymphoproliferative disease in a patient with rheumatoid arthritis. role of epstein-barr virus infection. *The Journal of Rheumatology*, 22, 1174-1178.
- Lofstrom, B., Backlin, C., Sundstrom, C., Ekbom, A. & Lundberg, I.E. (2007) A closer look at non-hodgkin's lymphoma cases in a national swedish systemic lupus erythematosus cohort: A nested case-control study. *Annals of the Rheumatic Diseases*, 66, 1627-1632.
- Loren, A.W., Porter, D.L., Stadtmauer, E.A. & Tsai, D.E. (2003) Post-transplant lymphoproliferative disorder: A review. *Bone Marrow Transplantation*, 31, 145-155.
- Lossos, I.S., Alizadeh, A.A., Rajapaksa, R., Tibshirani, R. & Levy, R. (2003) HGAL is a novel interleukin-4-inducible gene that strongly predicts survival in diffuse large B-cell lymphoma. *Blood*, 101, 433-440.
- Lu, X., Chen, J., Malumbres, R., Cubedo Gil, E., Helfman, D.M. & Lossos, I.S. (2007) HGAL, a lymphoma prognostic biomarker, interacts with the cytoskeleton and mediates the effects of IL-6 on cell migration. *Blood*, 110, 4268-4277.
- Mackay, F., Sierro, F., Grey, S.T. & Gordon, T.P. (2005) The BAFF/APRIL system: An important player in systemic rheumatic diseases. *Current Directions in Autoimmunity*, 8, 243-265.
- Mackay, F., Woodcock, S.A., Lawton, P., Ambrose, C., Baetscher, M., Schneider, P., Tschopp, J. & Browning, J.L. (1999) Mice transgenic for BAFF develop lymphocytic disorders along with autoimmune manifestations. *The Journal of Experimental Medicine*, 190, 1697-1710.
- Mackay, I.R. & Rose, N.R. (2001) Autoimmunity and lymphoma: Tribulations of B cells. *Nature Immunology*, 2, 793-795.
- Mackey, A.C., Green, L., Liang, L.C., Dinndorf, P. & Avigan, M. (2007) Hepatosplenic T cell lymphoma associated with infliximab use in young patients treated for inflammatory bowel disease. *Journal of Pediatric Gastroenterology and Nutrition*, 44, 265-267.
- Mariette, X. (1999) Lymphomas in patients with sjogren's syndrome: Review of the literature and physiopathologic hypothesis. *Leukemia & Lymphoma*, 33, 93-99.
- Mariette, X., Cazals-Hatem, D., Warszawski, J., Liote, F., Balandraud, N., Sibilia, J. & Investigators of the Club Rhumatismes et Inflammation. (2002) Lymphomas in rheumatoid arthritis patients treated with methotrexate: A 3-year prospective study in france. *Blood*, 99, 3909-3915.
- Mearin, M.L., Catassi, C., Brousse, N., Brand, R., Collin, P., Fabiani, E., Schweizer, J.J., Abuzakouk, M., Szajewska, H., Hallert, C., Farre Masip, C., Holmes, G.K. & Biomed Study Group on Coeliac Disease and Non-Hodgkin Lymphoma. (2006) European multi-centre study on coeliac disease and non-hodgkin lymphoma. *European Journal of Gastroenterology & Hepatology*, 18, 187-194.
- Meibohm, B., Beierle, I. & Derendorf, H. (2002) How important are gender differences in pharmacokinetics? *Clinical Pharmacokinetics*, 41, 329-342.
- Meijer, J.W., Mulder, C.J., Goerres, M.G., Boot, H. & Schweizer, J.J. (2004) Coeliac disease and (extra)intestinal T-cell lymphomas: Definition, diagnosis and treatment. *Scandinavian Journal of Gastroenterology. Supplement*, (241), 78-84.



- Mellemkjaer, L., Pfeiffer, R.M., Engels, E.A., Gridley, G., Wheeler, W., Hemminki, K., Olsen, J.H., Dreyer, L., Linet, M.S., Goldin, L.R. & Landgren, O. (2008) Autoimmune disease in individuals and close family members and susceptibility to non-hodgkin's lymphoma. *Arthritis and Rheumatism*, 58, 657-666.
- Mellors, R.C. (1966) Autoimmune disease in NZB-bl mice. II. autoimmunity and malignant lymphoma. *Blood*, 27, 435-448.
- Mention, J.J., Ben Ahmed, M., Begue, B., Barbe, U., Verkarre, V., Asnafi, V., Colombel, J.F., Cugnenc, P.H., Ruemmele, F.M., McIntyre, E., Brousse, N., Cellier, C. & Cerf-Bensussan, N. (2003) Interleukin 15: A key to disrupted intraepithelial lymphocyte homeostasis and lymphomagenesis in celiac disease. *Gastroenterology*, 125, 730-745.
- Miners, J.O., Grgurinovich, N., Whitehead, A.G., Robson, R.A. & Birkett, D.J. (1986) Influence of gender and oral contraceptive steroids on the metabolism of salicylic acid and acetylsalicylic acid. *British Journal of Clinical Pharmacology*, 22, 135-142.
- Moder, K.G., Tefferi, A., Cohen, M.D., Menke, D.M. & Luthra, H.S. (1995) Hematologic malignancies and the use of methotrexate in rheumatoid arthritis: A retrospective study. *The American Journal of Medicine*, 99, 276-281.
- Morton, J.E., Leyland, M.J., Vaughan Hudson, G., Vaughan Hudson, B., Anderson, L., Bennett, M.H. & MacLennan, K.A. (1993) Primary gastrointestinal non-hodgkin's lymphoma: A review of 175 british national lymphoma investigation cases. *British Journal of Cancer*, 67, 776-782.
- Moshynska, O.V. & Saxena, A. (2008) Clonal relationship between hashimoto thyroiditis and thyroid lymphoma. *Journal of Clinical Pathology*, 61, 438-444.
- Moss, K.E., Ioannou, Y., Sultan, S.M., Haq, I. & Isenberg, D.A. (2002) Outcome of a cohort of 300 patients with systemic lupus erythematosus attending a dedicated clinic for over two decades. *Annals of the Rheumatic Diseases*, 61, 409-413.
- Moutsopoulos, H.M., Steinberg, A.D., Fauci, A.S., Lane, H.C. & Papadopoulos, N.M. (1983) High incidence of free monoclonal lambda light chains in the sera of patients with sjogren's syndrome. *Journal of Immunology (Baltimore, Md.: 1950)*, 130, 2663-2665.
- Natkunam, Y., Lossos, I.S., Taidi, B., Zhao, S., Lu, X., Ding, F., Hammer, A.S., Marafioti, T., Byrne, G.E., Jr, Levy, S., Warnke, R.A. & Levy, R. (2005) Expression of the human germinal center-associated lymphoma (HGAL) protein, a new marker of germinal center B-cell derivation. *Blood*, 105, 3979-3986.
- Neumeister, P., Hoeffler, G., Beham-Schmid, C., Schmidt, H., Apfelbeck, U., Schaidler, H., Linkesch, W. & Sill, H. (1997) Deletion analysis of the p16 tumor suppressor gene in gastrointestinal mucosa-associated lymphoid tissue lymphomas. *Gastroenterology*, 112, 1871-1875.
- Ngo, V.N., Korner, H., Gunn, M.D., Schmidt, K.N., Riminton, D.S., Cooper, M.D., Browning, J.L., Sedgwick, J.D. & Cyster, J.G. (1999) Lymphotoxin alpha/beta and tumor necrosis factor are required for stromal cell expression of homing chemokines in B and T cell areas of the spleen. *The Journal of Experimental Medicine*, 189, 403-412.
- Niitsu, N., Okamoto, M., Nakamura, N., Nakamine, H., Bessho, M. & Hirano, M. (2007) Clinicopathologic correlations of stage IE/IIIE primary thyroid diffuse large B-cell lymphoma. *Annals of Oncology : Official Journal of the European Society for Medical Oncology / ESMO*, 18, 1203-1208.
- Nossent, J., Cikes, N., Kiss, E., Marchesoni, A., Nasonova, V., Mosca, M., Olesinska, M., Pokorný, G., Rozman, B., Schneider, M., Vlachoyiannopoulos, P.G. & Swaak, A.

- (2007) Current causes of death in systemic lupus erythematosus in europe, 2000--2004: Relation to disease activity and damage accrual. *Lupus*, 16, 309-317.
- Novakovic, B.J., Novakovic, S. & Frkovic-Grazio, S. (2006) A single-center report on clinical features and treatment response in patients with intestinal T cell non-hodgkin's lymphomas. *Oncology Reports*, 16, 191-195.
- Okada, T., Takiura, F., Tokushige, K., Nozawa, S., Kiyosawa, T., Nakauchi, H., Hirose, S. & Shirai, T. (1991) Major histocompatibility complex controls clonal proliferation of CD5+ B cells in H-2-congenic new zealand mice: A model for B cell chronic lymphocytic leukemia and autoimmune disease. *European Journal of Immunology*, 21, 2743-2748.
- Patey-Mariaud De Serre, N., Cellier, C., Jabri, B., Delabesse, E., Verkarre, V., Roche, B., Lavergne, A., Briere, J., Mauvieux, L., Leborgne, M., Barbier, J.P., Modigliani, R., Matuchansky, C., MacIntyre, E., Cerf-Bensussan, N. & Brousse, N. (2000) Distinction between coeliac disease and refractory sprue: A simple immunohistochemical method. *Histopathology*, 37, 70-77.
- Pedersen, R.K. & Pedersen, N.T. (1996) Primary non-hodgkin's lymphoma of the thyroid gland: A population based study. *Histopathology*, 28, 25-32.
- Picker, L.J. (1992) Mechanisms of lymphocyte homing. *Current Opinion in Immunology*, 4, 277-286.
- Pijpe, J., van Imhoff, G.W., Spijkervet, F.K., Roodenburg, J.L., Wolbink, G.J., Mansour, K., Vissink, A., Kallenberg, C.G. & Bootsma, H. (2005) Rituximab treatment in patients with primary sjogren's syndrome: An open-label phase II study. *Arthritis and Rheumatism*, 52, 2740-2750.
- Poole, B.D., Templeton, A.K., Guthridge, J.M., Brown, E.J., Harley, J.B. & James, J.A. (2009) Aberrant epstein-barr viral infection in systemic lupus erythematosus. *Autoimmunity Reviews*, 8, 337-342.
- Quartuccio, L., Fabris, M., Salvin, S., Maset, M., De Marchi, G. & De Vita, S. (2009) Controversies on rituximab therapy in sjogren syndrome-associated lymphoproliferation. *International Journal of Rheumatology*, 2009, 424935.
- Ramos-Casals, M., Brito-Zeron, P., Yague, J., Akasbi, M., Bautista, R., Ruano, M., Claver, G., Gil, V. & Font, J. (2005) Hypocomplementaemia as an immunological marker of morbidity and mortality in patients with primary sjogren's syndrome. *Rheumatology (Oxford, England)*, 44, 89-94.
- Randen, I., Mellbye, O.J., Forre, O. & Natvig, J.B. (1995) The identification of germinal centres and follicular dendritic cell networks in rheumatoid synovial tissue. *Scandinavian Journal of Immunology*, 41, 481-486.
- Ray, W.A. (2003) Population-based studies of adverse drug effects. *The New England Journal of Medicine*, 349, 1592-1594.
- Reunala, T. (1998) Dermatitis herpetiformis: Coeliac disease of the skin. *Annals of Medicine*, 30, 416-418.
- Reunala, T., Helin, H., Kuokkanen, K. & Hakala, T. (1982) Lymphoma in dermatitis herpetiformis: Report on four cases. *Acta Dermato-Venereologica*, 62, 343-346.
- Reunala, T., Blomqvist, K., Tarpila, S., Halme, H. & Kangas, K. (1977) Gluten-free diet in dermatitis herpetiformis. I. clinical response of skin lesions in 81 patients. *The British Journal of Dermatology*, 97, 473-480.

- Reyes, F., Lepage, E., Ganem, G., Molina, T.J., Brice, P., Coiffier, B., Morel, P., Ferme, C., Bosly, A., Lederlin, P., Laurent, G., Tilly, H. & Groupe d'Etude des Lymphomes de l'Adulte (GELA). (2005) ACVBP versus CHOP plus radiotherapy for localized aggressive lymphoma. *The New England Journal of Medicine*, 352, 1197-1205.
- Rizzi, R., Curci, P., Delia, M., Rinaldi, E., Chiefa, A., Specchia, G. & Liso, V. (2009) Spontaneous remission of "methotrexate-associated lymphoproliferative disorders" after discontinuation of immunosuppressive treatment for autoimmune disease. review of the literature. *Medical Oncology (Northwood, London, England)*, 26, 1-9.
- Rosenberg, L., Palmer, J.R., Zauber, A.G., Warshauer, M.E., Strom, B.L., Harlap, S. & Shapiro, S. (1995) Relation of benzodiazepine use to the risk of selected cancers: Breast, large bowel, malignant melanoma, lung, endometrium, ovary, non-hodgkin's lymphoma, testis, hodgkin's disease, thyroid, and liver. *American Journal of Epidemiology*, 141, 1153-1160.
- Rosenthal, A.K., McLaughlin, J.K., Gridley, G. & Nyren, O. (1995) Incidence of cancer among patients with systemic sclerosis. *Cancer*, 76, 910-914.
- Rosenthal, A.K., McLaughlin, J.K., Linet, M.S. & Persson, I. (1993) Scleroderma and malignancy: An epidemiological study. *Annals of the Rheumatic Diseases*, 52, 531-533.
- Rossi, D. (2009) Thyroid lymphoma: Beyond antigen stimulation. *Leukemia Research*, 33, 607-609.
- Roumm, A.D. & Medsger, T.A., Jr. (1985) Cancer and systemic sclerosis. an epidemiologic study. *Arthritis and Rheumatism*, 28, 1336-1340.
- Royer, B., Cazals-Hatem, D., Sibilia, J., Agbalika, F., Cayuela, J.M., Soussi, T., Maloisel, F., Clauvel, J.P., Brouet, J.C. & Mariette, X. (1997) Lymphomas in patients with sjogren's syndrome are marginal zone B-cell neoplasms, arise in diverse extranodal and nodal sites, and are not associated with viruses. *Blood*, 90, 766-775.
- Ruggiero, F.P., Frauenhoffer, E. & Stack, B.C., Jr. (2005) Thyroid lymphoma: A single institution's experience. *Otolaryngology--Head and Neck Surgery : Official Journal of American Academy of Otolaryngology-Head and Neck Surgery*, 133, 888-896.
- Salloum, E., Cooper, D.L., Howe, G., Lacy, J., Tallini, G., Crouch, J., Schultz, M. & Murren, J. (1996) Spontaneous regression of lymphoproliferative disorders in patients treated with methotrexate for rheumatoid arthritis and other rheumatic diseases. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology*, 14, 1943-1949.
- Sato, S., Fujimoto, M., Hasegawa, M. & Takehara, K. (2004) Altered blood B lymphocyte homeostasis in systemic sclerosis: Expanded naive B cells and diminished but activated memory B cells. *Arthritis and Rheumatism*, 50, 1918-1927.
- Savilahti, E., Reunala, T. & Maki, M. (1992) Increase of lymphocytes bearing the gamma/delta T cell receptor in the jejunum of patients with dermatitis herpetiformis. *Gut*, 33, 206-211.
- Saxena, A., Alport, E.C., Moshynska, O., Kanthan, R. & Boctor, M.A. (2004) Clonal B cell populations in a minority of patients with hashimoto's thyroiditis. *Journal of Clinical Pathology*, 57, 1258-1263.
- Schroder, A.E., Greiner, A., Seyfert, C. & Berek, C. (1996) Differentiation of B cells in the nonlymphoid tissue of the synovial membrane of patients with rheumatoid arthritis. *Proceedings of the National Academy of Sciences of the United States of America*, 93, 221-225.
- Setoguchi, S., Solomon, D.H., Weinblatt, M.E., Katz, J.N., Avorn, J., Glynn, R.J., Cook, E.F., Carney, G. & Schneeweiss, S. (2006) Tumor necrosis factor alpha antagonist use and cancer in patients with rheumatoid arthritis. *Arthritis and Rheumatism*, 54, 2757-2764.

- Seyler, T.M., Park, Y.W., Takemura, S., Bram, R.J., Kurtin, P.J., Goronzy, J.J. & Weyand, C.M. (2005) BLYS and APRIL in rheumatoid arthritis. *The Journal of Clinical Investigation*, 115, 3083-3092.
- Siau, K., Laversuch, C.J., Creamer, P. & O'Rourke, K.P. (2010) Malignancy in scleroderma patients from south west england: A population-based cohort study. *Rheumatology International*.
- Sieniawski, M., Angamuthu, N., Boyd, K., Chasty, R., Davies, J., Forsyth, P., Jack, F., Lyons, S., Mounter, P., Revell, P., Proctor, S.J. & Lennard, A.L. (2010) Evaluation of enteropathy-associated T-cell lymphoma comparing standard therapies with a novel regimen including autologous stem cell transplantation. *Blood*, 115, 3664-3670.
- Sigurgeirsson, B., Agnarsson, B.A. & Lindelof, B. (1994) Risk of lymphoma in patients with dermatitis herpetiformis. *BMJ (Clinical Research Ed.)*, 308, 13-15.
- Silano, M., Volta, U., Vincenzi, A.D., Dessi, M., Vincenzi, M.D. & Collaborating Centers of the Italian Registry of the Complications of Coeliac Disease. (2008) Effect of a gluten-free diet on the risk of enteropathy-associated T-cell lymphoma in celiac disease. *Digestive Diseases and Sciences*, 53, 972-976.
- Silano, M., Volta, U., Mecchia, A.M., Dessi, M., Di Benedetto, R., De Vincenzi, M. & Collaborating centers of the Italian registry of the complications of coeliac disease. (2007) Delayed diagnosis of coeliac disease increases cancer risk. *BMC Gastroenterology*, 7, 8.
- Simon, Z., Tarr, T., Ress, Z., Gergely, L., Kiss, E. & Illes, A. (2007) Successful rituximab-CHOP treatment of systemic lupus erythematosus associated with diffuse large B-cell non-hodgkin lymphoma. *Rheumatology International*, 28, 179-183.
- Skopouli, F.N., Dafni, U., Ioannidis, J.P. & Moutsopoulos, H.M. (2000) Clinical evolution, and morbidity and mortality of primary sjogren's syndrome. *Seminars in Arthritis and Rheumatism*, 29, 296-304.
- Smedby, K.E., Baecklund, E. & Askling, J. (2006) Malignant lymphomas in autoimmunity and inflammation: A review of risks, risk factors, and lymphoma characteristics. *Cancer Epidemiology, Biomarkers & Prevention : A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology*, 15, 2069-2077.
- Smedby, K.E., Askling, J., Mariette, X. & Baecklund, E. (2008) Autoimmune and inflammatory disorders and risk of malignant lymphomas--an update. *Journal of Internal Medicine*, 264, 514-527.
- Smedby, K.E., Akerman, M., Hildebrand, H., Glimelius, B., Ekblom, A. & Askling, J. (2005) Malignant lymphomas in coeliac disease: Evidence of increased risks for lymphoma types other than enteropathy-type T cell lymphoma. *Gut*, 54, 54-59.
- Smedby, K.E., Hjalgrim, H., Askling, J., Chang, E.T., Gregersen, H., Porwit-MacDonald, A., Sundstrom, C., Akerman, M., Melbye, M., Glimelius, B. & Adami, H.O. (2006) Autoimmune and chronic inflammatory disorders and risk of non-hodgkin lymphoma by subtype. *Journal of the National Cancer Institute*, 98, 51-60.
- Soderberg, K.C., Jonsson, F., Winqvist, O., Hagmar, L. & Feychting, M. (2006) Autoimmune diseases, asthma and risk of haematological malignancies: A nationwide case-control study in sweden. *European Journal of Cancer (Oxford, England : 1990)*, 42, 3028-3033.
- Soderstrom, N., Axelsson, J.A. & Hagelqvist, E. (1970) Postcapillary venules of the lymph node type in the thymus in myasthenia. *Laboratory Investigation; a Journal of Technical Methods and Pathology*, 23, 451-458.

- Soldini, D., Mora, O., Cavalli, F., Zucca, E. & Mazzucchelli, L. (2008) Efficacy of alemtuzumab and gemcitabine in a patient with enteropathy-type T-cell lymphoma. *British Journal of Haematology*, 142, 484-486.
- Sorensen, H.T., Friis, S., Norgard, B., Mellekjaer, L., Blot, W.J., McLaughlin, J.K., Ekbo, A. & Baron, J.A. (2003) Risk of cancer in a large cohort of nonaspirin NSAID users: A population-based study. *British Journal of Cancer*, 88, 1687-1692.
- Staunton, M.D. & Greening, W.P. (1973) Clinical diagnosis of thyroid cancer. *British Medical Journal*, 4, 532-535.
- Stott, D.I., Hiepe, F., Hummel, M., Steinhauser, G. & Berek, C. (1998) Antigen-driven clonal proliferation of B cells within the target tissue of an autoimmune disease. the salivary glands of patients with sjogren's syndrome. *The Journal of Clinical Investigation*, 102, 938-946.
- Su, L. & David, M. (1999) Inhibition of B cell receptor-mediated apoptosis by IFN. *Journal of Immunology (Baltimore, Md.: 1950)*, 162, 6317-6321.
- Swerdlow, S.H., Campo, E., Harris, N.L., Jaffe, E.S., Pileri, S., Stein, H., Thiele, J. & Vardiman J.W. (2008) WHO classification of tumours of haematopoietic and lymphoid tissues.
- Symmons, D.P. (1985) Neoplasms of the immune system in rheumatoid arthritis. *The American Journal of Medicine*, 78, 22-28.
- Szekanecz, E., Szamosi, S., Gergely, L., Keszthelyi, P., Szekanecz, Z. & Szucs, G. (2008) Incidence of lymphoma in systemic sclerosis: A retrospective analysis of 218 hungarian patients with systemic sclerosis. *Clinical Rheumatology*, 27, 1163-1166.
- Szodoray, P. & Jonsson, R. (2005) The BAFF/APRIL system in systemic autoimmune diseases with a special emphasis on sjogren's syndrome. *Scandinavian Journal of Immunology*, 62, 421-428.
- Tack, G.J., Verbeek, W.H., Schreurs, M.W. & Mulder, C.J. (2010a) The spectrum of celiac disease: Epidemiology, clinical aspects and treatment. *Nature Reviews. Gastroenterology & Hepatology*, 7, 204-213.
- Tack, G.J., Wondergem, M.J., Al-Toma, A., Verbeek, W.H., Schmittel, A., Machado, M.V., Perri, F., Ossenkoppele, G.J., Huijgens, P.C., Schreurs, M.W., Mulder, C.J. & Visser, O.J. (2010b) Auto-SCT in refractory celiac disease type II patients unresponsive to cladribine therapy. *Bone Marrow Transplantation*, .
- Takakuwa, T., Miyauchi, A. & Aozasa, K. (2009) Aberrant somatic hypermutations in thyroid lymphomas. *Leukemia Research*, 33, 649-654.
- Tamura, K., Shimaoka, K. & Friedman, M. (1981) Thyroid abnormalities associated with treatment of malignant lymphoma. *Cancer*, 47, 2704-2711.
- Tan, L.C., Mowat, A.G., Fazou, C., Rostron, T., Roskell, H., Dunbar, P.R., Tournay, C., Romagne, F., Peyrat, M.A., Houssaint, E., Bonneville, M., Rickinson, A.B., McMichael, A.J. & Callan, M.F. (2000) Specificity of T cells in synovial fluid: High frequencies of CD8(+) T cells that are specific for certain viral epitopes. *Arthritis Research*, 2, 154-164.
- Tapinos, N.I., Polihronis, M. & Moutsopoulos, H.M. (1999) Lymphoma development in sjogren's syndrome: Novel p53 mutations. *Arthritis and Rheumatism*, 42, 1466-1472.
- Thanou-Stavraki, A. & Sawalha, A.H. (2011) An update on belimumab for the treatment of lupus. *Biologics : Targets & Therapy*, 5, 33-43.
- Theander, E., Manthorpe, R. & Jacobsson, L.T. (2004) Mortality and causes of death in primary sjogren's syndrome: A prospective cohort study. *Arthritis and Rheumatism*, 50, 1262-1269.

- Theander, E., Henriksson, G., Ljungberg, O., Mandl, T., Manthorpe, R. & Jacobsson, L.T. (2006) Lymphoma and other malignancies in primary sjogren's syndrome: A cohort study on cancer incidence and lymphoma predictors. *Annals of the Rheumatic Diseases*, 65, 796-803.
- Theofilopoulos, A.N., Baccala, R., Beutler, B. & Kono, D.H. (2005) Type I interferons (alpha/beta) in immunity and autoimmunity. *Annual Review of Immunology*, 23, 307-336.
- Thieblemont, C., Mayer, A., Dumontet, C., Barbier, Y., Callet-Bauchu, E., Felman, P., Berger, F., Ducottet, X., Martin, C., Salles, G., Orgiazzi, J. & Coiffier, B. (2002) Primary thyroid lymphoma is a heterogeneous disease. *The Journal of Clinical Endocrinology and Metabolism*, 87, 105-111.
- Tincani, A., Taraborelli, M. & Cattaneo, R. (2010) Antiphospholipid antibodies and malignancies. *Autoimmunity Reviews*, 9, 200-202.
- Tosato, G., Steinberg, A.D. & Blaese, R.M. (1981) Defective EBV-specific suppressor T-cell function in rheumatoid arthritis. *The New England Journal of Medicine*, 305, 1238-1243.
- Tosato, G., Steinberg, A.D., Yarchoan, R., Heilman, C.A., Pike, S.E., De Seau, V. & Blaese, R.M. (1984) Abnormally elevated frequency of epstein-barr virus-infected B cells in the blood of patients with rheumatoid arthritis. *The Journal of Clinical Investigation*, 73, 1789-1795.
- Toubi, E. & Shoenfeld, Y. (2007) Clinical and biological aspects of anti-P-ribosomal protein autoantibodies. *Autoimmunity Reviews*, 6, 119-125.
- Troch, M., Woehrer, S., Streubel, B., Weissel, M., Hoffmann, M., Mullauer, L., Chott, A. & Raderer, M. (2008) Chronic autoimmune thyroiditis (hashimoto's thyroiditis) in patients with MALT lymphoma. *Annals of Oncology : Official Journal of the European Society for Medical Oncology / ESMO*, 19, 1336-1339.
- Tsang, R.W., Gospodarowicz, M.K., Pintilie, M., Wells, W., Hodgson, D.C., Sun, A., Crump, M. & Patterson, B.J. (2003) Localized mucosa-associated lymphoid tissue lymphoma treated with radiation therapy has excellent clinical outcome. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology*, 21, 4157-4164.
- Tupchong, L., Hughes, F. & Harmer, C.L. (1986) Primary lymphoma of the thyroid: Clinical features, prognostic factors, and results of treatment. *International Journal of Radiation Oncology, Biology, Physics*, 12, 1813-1821.
- Tureson, C. & Matteson, E.L. (2004) Management of extra-articular disease manifestations in rheumatoid arthritis. *Current Opinion in Rheumatology*, 16, 206-211.
- Tzioufas, A.G., Boumba, D.S., Skopouli, F.N. & Moutsopoulos, H.M. (1996) Mixed monoclonal cryoglobulinemia and monoclonal rheumatoid factor cross-reactive idiotypes as predictive factors for the development of lymphoma in primary sjogren's syndrome. *Arthritis and Rheumatism*, 39, 767-772.
- Tzioufas, A.G., Manoussakis, M.N., Costello, R., Silis, M., Papadopoulos, N.M. & Moutsopoulos, H.M. (1986) Cryoglobulinemia in autoimmune rheumatic diseases. evidence of circulating monoclonal cryoglobulins in patients with primary sjogren's syndrome. *Arthritis and Rheumatism*, 29, 1098-1104.
- Valesini, G., Priori, R., Bavoillot, D., Osborn, J., Danieli, M.G., Del Papa, N., Gerli, R., Pietrogrande, M., Sabbadini, M.G., Silvestris, F. & Valsecchi, L. (1997) Differential risk of non-hodgkin's lymphoma in italian patients with primary sjogren's syndrome. *The Journal of Rheumatology*, 24, 2376-2380.
- Vallabhapurapu, S. & Karin, M. (2009) Regulation and function of NF-kappaB transcription factors in the immune system. *Annual Review of Immunology*, 27, 693-733.

- van de Water, J.M., Cillessen, S.A., Visser, O.J., Verbeek, W.H., Meijer, C.J. & Mulder, C.J. (2010) Enteropathy associated T-cell lymphoma and its precursor lesions. *Best Practice & Research. Clinical Gastroenterology*, 24, 43-56.
- Veeranki, S. & Choubey, D. (2010) Systemic lupus erythematosus and increased risk to develop B cell malignancies: Role of the p200-family proteins. *Immunology Letters*, 133, 1-5.
- Verdolini, R., Bugatti, L., Giangiacomini, M., Nicolini, M., Filosa, G. & Cerio, R. (2002) Systemic lupus erythematosus induced by epstein-barr virus infection. *The British Journal of Dermatology*, 146, 877-881.
- Verkarre, V., Romana, S.P., Cellier, C., Asnafi, V., Mention, J.J., Barbe, U., Nusbaum, S., Hermine, O., Macintyre, E., Brousse, N., Cerf-Bensussan, N. & Radford-Weiss, I. (2003) Recurrent partial trisomy 1q22-q44 in clonal intraepithelial lymphocytes in refractory celiac sprue. *Gastroenterology*, 125, 40-46.
- Vettori, S., Staibano, S., Mascolo, M., Ilardi, G. & Valentini, G. (2010) Non-hodgkin's lymphoma in systemic sclerosis: Case and literature review. *Clinical Rheumatology*, 29, 1-6.
- Viljamaa, M., Kaukinen, K., Pukkala, E., Hervonen, K., Reunala, T. & Collin, P. (2006) Malignancies and mortality in patients with coeliac disease and dermatitis herpetiformis: 30-year population-based study. *Digestive and Liver Disease : Official Journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver*, 38, 374-380.
- Vivas, S., Ruiz de Morales, J.M., Ramos, F. & Suarez-Vilela, D. (2006) Alemtuzumab for refractory celiac disease in a patient at risk for enteropathy-associated T-cell lymphoma. *The New England Journal of Medicine*, 354, 2514-2515.
- von Roon, A.C., Reese, G., Teare, J., Constantinides, V., Darzi, A.W. & Tekkis, P.P. (2007) The risk of cancer in patients with crohn's disease. *Diseases of the Colon and Rectum*, 50, 839-855.
- Voulgarelis, M., Giannouli, S., Tzioufas, A.G. & Moutsopoulos, H.M. (2006) Long term remission of sjogren's syndrome associated aggressive B cell non-hodgkin's lymphomas following combined B cell depletion therapy and CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone). *Annals of the Rheumatic Diseases*, 65, 1033-1037.
- Voulgarelis, M., Petroustos, G., Moutsopoulos, H.M. & Skopouli, F.N. (2002) 2-chloro-2'-deoxyadenosine in the treatment of sjogren's syndrome-associated B cell lymphoproliferation. *Arthritis and Rheumatism*, 46, 2248-2249.
- Voulgarelis, M., Dafni, U.G., Isenberg, D.A. & Moutsopoulos, H.M. (1999) Malignant lymphoma in primary sjogren's syndrome: A multicenter, retrospective, clinical study by the european concerted action on sjogren's syndrome. *Arthritis and Rheumatism*, 42, 1765-1772.
- Wang, S.A., Rahemtullah, A., Faquin, W.C., Roepke, J., Harris, N.L. & Hasserjian, R.P. (2005) Hodgkin's lymphoma of the thyroid: A clinicopathologic study of five cases and review of the literature. *Modern Pathology : An Official Journal of the United States and Canadian Academy of Pathology, Inc*, 18, 1577-1584.
- Watanabe-Fukunaga, R., Brannan, C.I., Copeland, N.G., Jenkins, N.A. & Nagata, S. (1992) Lymphoproliferation disorder in mice explained by defects in fas antigen that mediates apoptosis. *Nature*, 356, 314-317.
- Watson, W.C., Tooms, R.E., Carnesale, P.G. & Dutkowsky, J.P. (1994) A case of germinal center formation by CD45RO T and CD20 B lymphocytes in rheumatoid arthritic

- subchondral bone: Proposal for a two-compartment model of immune-mediated disease with implications for immunotherapeutic strategies. *Clinical Immunology and Immunopathology*, 73, 27-37.
- Weetman, A.P. & McGregor, A.M. (1994) Autoimmune thyroid disease: Further developments in our understanding. *Endocrine Reviews*, 15, 788-830.
- Weinblatt, M.E., Maier, A.L., Fraser, P.A. & Coblyn, J.S. (1998) Longterm prospective study of methotrexate in rheumatoid arthritis: Conclusion after 132 months of therapy. *The Journal of Rheumatology*, 25, 238-242.
- Weyand, C.M., Goronzy, J.J. & Kurtin, P.J. (2006) Lymphoma in rheumatoid arthritis: An immune system set up for failure. *Arthritis and Rheumatism*, 54, 685-689.
- Wolfe, F. & Michaud, K. (2007) The effect of methotrexate and anti-tumor necrosis factor therapy on the risk of lymphoma in rheumatoid arthritis in 19,562 patients during 89,710 person-years of observation. *Arthritis and Rheumatism*, 56, 1433-1439.
- Wolfe, F. & Michaud, K. (2004) Lymphoma in rheumatoid arthritis: The effect of methotrexate and anti-tumor necrosis factor therapy in 18,572 patients. *Arthritis and Rheumatism*, 50, 1740-1751.
- Wright, D.H. (1995) The major complications of coeliac disease. *Bailliere's Clinical Gastroenterology*, 9, 351-369.
- Xin, H., D'Souza, S., Jorgensen, T.N., Vaughan, A.T., Lengyel, P., Kotzin, B.L. & Choubey, D. (2006) Increased expression of Ifi202, an IFN-activatable gene, in B6.Nba2 lupus susceptible mice inhibits p53-mediated apoptosis. *Journal of Immunology (Baltimore, Md.: 1950)*, 176, 5863-5870.
- Xu, Y. & Wiernik, P.H. (2001) Systemic lupus erythematosus and B-cell hematologic neoplasm. *Lupus*, 10, 841-850.
- Yao, Q.Y., Rickinson, A.B., Gaston, J.S. & Epstein, M.A. (1986) Disturbance of the epstein-barr virus-host balance in rheumatoid arthritis patients: A quantitative study. *Clinical and Experimental Immunology*, 64, 302-310.
- Youinou, P., Devauchelle-Pensec, V. & Pers, J.O. (2010) Significance of B cells and B cell clonality in sjogren's syndrome. *Arthritis and Rheumatism*, 62, 2605-2610.
- Youinou, P., Papadopoulos, N.M., Katsikis, P., Pennec, Y.L., Jouquan, J., Lelong, A. & Moutsopoulos, H.M. (1988) Monoclonal immunoglobulins in the serum of patients with primary sjogren's syndrome. *Clinical and Experimental Rheumatology*, 6, 247-252.
- Young, L.S. & Rickinson, A.B. (2004) Epstein-barr virus: 40 years on. *Nature Reviews.Cancer*, 4, 757-768.
- Zatuchni, J., Campbell, W.N. & Zarafonitis, C.J. (1953) Pulmonary fibrosis and terminal bronchiolar (alveolar-cell) carcinoma in scleroderma. *Cancer*, 6, 1147-1158.
- Zhang, Y., Holford, T.R., Leaderer, B., Zahm, S.H., Boyle, P., Morton, L.M., Zhang, B., Zou, K., Flynn, S., Tallini, G., Owens, P.H. & Zheng, T. (2004) Prior medical conditions and medication use and risk of non-hodgkin lymphoma in connecticut united states women. *Cancer Causes & Control* : CCC, 15, 419-428.
- Zintzaras, E., Voulgarelis, M. & Moutsopoulos, H.M. (2005) The risk of lymphoma development in autoimmune diseases: A meta-analysis. *Archives of Internal Medicine*, 165, 2337-2344.



© 2011 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the [Creative Commons Attribution 3.0 License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.