Scientific Literature

- CD4 Cells
- Ataxia Telangiectasia
- CGD
- Malnutrition
- HIV Virus
- TB Drugs
- HLA
- Hyper IgM Syndrome
- Inflammatory Bowel Disease
- Ankylosing spondylitis
- Acute Retroviral Syndrome
- Ulcerative Colitis

Literature on CD4 Cells

CD4 help regulates expression of crucial genes involved in CD8 T cell memory and sensitivity to regulatory elements.

J Immunol. 2008 Jul 1;181(1):299-308
Rapetti L, Meunier S, Pontoux C, Tanchot C.

Although the role of **CD4** help during memory differentiation has been clearly demonstrated, the mechanisms involved to mediate CD4 help is unknown. In this study, gene analysis shows that unhelped CD8 cells have defects in their three main characteristics of expression; proliferation, survival and cytotoxic functions. This shows that CD4 cells have multiple effects on CD8 memory differentiation.

Link to PubMed abstract

CD4 Percentages and Total Lymphocyte Counts as Early Surrogate Markers for Pediatric HIV-1 Infection in Resource-Limited Settings.

ournal of Tropical Pediatrics, 2006 Oct; 52: 346-354.
F Rouet,, A Inwoley, D Ekouevi, I Viho, R Becquet, C Sakarovitch, L Bequet, B Tonwe-Gold, ML Chaix, V Leroy, C Rouzioux, F Dabis and the ANRS 1201/1202 Ditrame Plus Study Group.

This paper looks at %CD4 and total **lymphocyte** count (TLC) in African children born to HIV-1-infected mothers as useful markers of HIV infection. The authors show data where at 3 months after birth, a

threshold of 25% CD4 cells could be used to distinguish HIV infection from those children who were not HIV infected. TLC was of no value. Interesting paper, showing that %CD4 maybe a sensitive cost-effective alternative to plasma RNA copies.

Link to PubMed abstract
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Evidence for extrathymic T cell maturation after thymectomy in infancy.

Clinical and Experimental Immunology, 2006 Sep;145(3):407-12.
Torfadottir H, Freysdottir J, Skaftadottir I, Haraldsson A, Sigfusson G, Ogmundsdottir HM.

This is an interesting paper that looks at extrathymic T cell maturation. Although limited in numbers, this study was able to investigate 8 infants who were thymectomized during heart surgery and compare T cell subsets with control children who were sex and age-matched. Cell subsets were looked at using flow cytometry using panels of antibodies measuring naïve, memory, activated and regulatory T cell markers. Authors conclude that some T cell phenotypes, notably T regulatory subsets, can mature without a thymus.

Link to PubMed abstract

Increased CD154 Expression in Uninfected Infants Born to HIV-Positive Mothers Exposed to Antiretroviral Prophylaxis.

Viral Immunology, 2006 Sep;19(3):363-72.
Romano MF, Buffolano W, Bisogni R, Russo R, Liuzzi R, Bunders M, Newell ML, Giarrusso PC.

This paper studies the immunostimulatory effects of ART in uninfected HIV-exposed infants receiving either ante- or postnatal therapy. They found that CD4(+) and CD8(+) lymphocytes of HIV-exposed noninfected infants who have been exposed to antiretroviral drugs in foetal life and early life display enhanced CD154 expression on both subsets. Although there was no T cell functional tests performed, it is possible this may mean increased T helper function in response to ART in uninfected infants?

Link to PubMed abstract
Link to full text

Within and between race differences in lymphocyte, CD4+, CD8+ and neutrophil levels in HIV-uninfected children with or without HIV exposure in Europe and Uganda.

Annals of Tropical Paediatrics, 2006 Sep;26(3):169-79
Bunders M, Lugada E, Mermin J, Downing R, Were W, Thorne C, Newell ML; European Collaborative Study.

This paper looks at large numbers of children born and living in Europe and those children born and living in Uganda, age, gender and genetically matched (children born to Ugandan mothers). Differential counts, total lymphocyte counts and %CD4 and %CD8 T cells were compared. They found differences in neutrophils and %CD4 cells, being lower in children living in Uganda. The authors conclude that nutrition and exposure to micro-organisms affect the developing immune system and account for these differences.

Link to PubMed abstract
Link to full text

Risk factors for opportunistic illnesses in children with human immunodeficiency virus in the era of highly active antiretroviral therapy.

Archives of Pediatric Adolescent Medicine, 2006 Aug;160(8):778-87.
Ylitalo N, Brogly S, Hughes MD, Nachman S, Dankner W, Van Dyke R, Seage GR 3rd; Pediatric AIDS Clincial Trials Group Protocol 219C Team.

This paper studies the relationship of HAART and opportunistic infections among 1927 children who were perinataly infected with HIV. They found that a low % CD4 T lymphocytes and a lack of sustained response to HAART, rather than the age or duration of drug treatment, was significantly predictive of opportunistic infection risks.

Link to PubMed abstract
Link to full text

Administration of Live Varicella Vaccine to HIV-Infected Children with Current or Past Significant Depression of CD4+ T Cells

Journal of Infect Diseases, 2006 Jul 15;194(2):247-55.
Levin MJ, Gershon AA, Weinberg A, Song LY, Fentin T, Nowak B. Pediatric AIDS Clinical Trials Group 265 Team.

This paper explores the vexing issue of immunizing HIV positive children against chicken pox and at what level of CD4 counts would be safe. Children ranging from 1-8 years of age and who had never had chicken pox before (naïve for Varicella Zoster virus, VSV) were given varicella vaccine. The authors show that regardless of CD4 counts in the children, the vaccine was well tolerated and 80% of HIV positive children made antibodies. Thus, children infected with HIV would probably be protected (by the production of antibodies), with a CD4 percent of greater than or equal to 15% and a **CD4 count** of equal to or greater than 200 cells.

Link to PubMed abstract
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Predictive value of absolute CD4 cell count for disease progression in untreated HIV-1-infected children. HIV Paediatric Prognostic Markers Collaborative Study.

AIDS 2006 Jun;20(9):1289-94

This study looks at the risk to progression to AIDS and death within 12 months by investigating absolute CD4 counts. In children older than 4-5 years of age the risk of disease progression increased when the CD4 count fell below 200-330 cells/microl, although the CD4 cell count was less prognostic in younger children. The authors conclude that CD4 criteria used in adults can be extended to children from 4-5 years of age, but not younger.

Link to PubMed abstract

Outcomes for human immunodeficiency virus-1-infected infants in the United kingdom and Republic of Ireland in the era of effective antiretroviral therapy.

Pediatric Infectious Disease Journal, 2006 May;25(5):420-6.
Doerholt K, Duong T, Tookey P, Butler K, Lyall H, Sharland M, Novelli V, Riordan A, Dunn D, Walker AS, Gibb DM. Collaborative HIV Paediatric Study.

This paper looks at the progression of AIDS and the subsequent death of infected infants in the era of ARV since 1997. CD4 and HIV-1 RNA responses were assessed in 481 infants and the paper shows data where mortality was lowered by giving HAART, but symptomatic disease rates remain high.

Link to PubMed abstract

European Collaborative Study. CD4 cell response to antiretroviral therapy in children with vertically acquired HIV infection: is it associated with age at initiation?

Journal of Infectious Diseases, 2006 Apr 1;193(7):954-62
Newell ML, Patel D, Goetghebuer T, Thorne C.

This paper explores the early initiation of ART in children and comes from the European Collaborative Study. The study took 131 children ranging from 0.1 to 15 years and showed that there was a benefit of initiating ART before 5 months of age. This appeared to result in a sustained recovery of the CD4 count. Lots of statistics.

Link to PubMed abstract
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Evaluation of p24-based antiretroviral treatment monitoring in pediatric HIV-1 infection: prediction of the CD4+ T-cell changes between consecutive visits.

Journal of Acquired Immune Deficiency Syndrome, 2006 Apr 15;41(5):557-62.
Brinkhof MW, Boni J, Steiner F, Tomasik Z, Nadal D, Schupbach J.

This paper looks at cheaper and affordable methods of evaluating the effectiveness of ART, rather than measuring viral load. This was a small study of 24 children followed over 5 years of ART. Viral loads were measured in parallel with an ultra sensitive p24 assay in heated plasma. The findings appear a bit ambiguous, but the authors conclude that p24 may be more accurate than measuring **viral load** and certainly cheaper.

Link to PubMed abstract
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Association of CD4+ T-lymphocyte counts and new thymic emigrants in HIV-infected children during successful highly active antiretroviral therapy

Journal of Allergy Clinical Immunology, 2006 Apr;117(4):748-52.
Saitoh A, Singh KK, Sandall S, Powell CA, Fenton T, Fletcher CV, Hsia K, Spector SA.

This paper provides evidence that new T cells arrive in the blood circulation when children are treated with ART. This was measured by looking at T cell receptor excision circles (TRECs), which indicate recently recruited T cells from the thymus gland. The authors made associations with levels of HIV DNA and the levels of TREC and conclude that the thymus gland is active in producing new CD4 cells when HIV DNA levels are high during ART. The conclusion is that TREC levels are a useful marker of thymus gland function in HIV infected children.

Link to PubMed abstract
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The First 5 Years of the Family Clinic for HIV at Tygerberg Hospital: Family Demographics, Survival of Children and Early Impact of Antiretroviral Therapy

Journal of Tropical Pediatrics, 2006 Feb; 52(1):3-11
N van Kooten Niekerk, M. Knies, J. Howard, H. Rabie, M. Zeier, A. van Rensburg, N. Frans, HS Schaaf, G. Fatti, F. Little and MF Cotton.

This study was aimed at children attending the Family Clinic at Tygerberg Academic Hospital. They study the factors that affect disease progression in children. 432 children were tested and the majority of these children were malnourished. 47 percent of these children were in clinical stage B and two-thirds had moderate or severe CD4 (+) T cell depletion.

Link to PubMed abstract
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Literature on Ataxia Telangiectasia

Screening for ATM sequence alterations in African-American women diagnosed with breast cancer.

Breast Cancer Research and Treatment, 2008 Jan;107(1):139-44. Epub 2007 Feb 27.
Hirsch AE, Atencio DP, Rosenstein BS.

Women who are heterozygous for variants in the ataxia telangiectasia mutated (ATM) gene, ATM carriers, have been reported to be at increased risk for breast cancer compared with women who do not posses an alteration in this gene. Aside from BRCA1 and BRCA2, there is little data on breast cancer susceptibility genes in African-American women. The goal of this study was to determine whether there is evidence that ATM is a breast cancer susceptibility gene in African-American women.

Link to Pubmed abstract
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Pulmonary function in adolescents with ataxia telangiectasia.

Paediatric Pulmonolgy, 2008 Jan;43(1):59-66.
McGrath-Morrow S, Lefton-Greif M, Rosquist K, Crawford T, Kelly A, Zeitlin P, Carson KA, Lederman HM.

Pulmonary complications are common in adolescents with ataxia telangiectasia (A-T), however objective measurements of lung function are difficult to obtain because of underlying bulbar weakness, tremors, and difficulty coordinating voluntary respiratory manoeuvres. Spirometry testing was found to be reproducible in A-T adolescents suggesting that spirometry testing may be useful for tracking changes in pulmonary function over time in this population.

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Two-stage case-control study of common ATM gene variants in relation to

breast cancer risk.

Breast cancer research and treatment 2007 Nov;106(1):121-6.
Epub 2007 Mar 13

The ataxia telangiectasia mutated (ATM) gene is a tumor suppressor gene that plays a critical role in cell cycle arrest, apoptosis, and DNA repair. In this study researchers evaluated two reported nonsynonymous SNPs and three additional common gene variants in the ATM gene in relation to breast cancer risk.

Link to Pubmed abstract
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Rapid molecular prenatal diagnosis of ataxia-telangiectasia by direct mutational analysis.

Prenatal Diagnosis, 2007 Sep;27(9):861-4.
Mancebo E, Bernardo I, Castro MJ, Fernández-Martinez FJ, Barreiro E, De-Pablos P, Marin MJ, Cortezon S, Paz-Artal E, Allende LM.

Mutations of the ataxia-telangiectasia-mutated (ATM) gene are responsible for the autosomal recessive disorder ataxia-telangiectasia (A-T). This study reports the first A-T prenatal diagnosis performed in Spain by direct molecular analysis. The ability to identify ATM mutations provides a tool that can be applied in confirmatory diagnosis, genetic counselling, carrier prediction and prenatal diagnosis.

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Ataxia-telangiectasia: mild neurological presentation despite null ATM mutation and severe cellular phenotype.

American Journal of Medical Genetics, 2007 Aug 15;143(16):1827-34.
Alterman N, Fattal-Valevski A, Moyal L, Crawford TO, Lederman HM, Ziv Y, Shiloh Y.

Ataxia-telangiectasia (A-T) is an autosomal recessive disorder characterized by progressive neurodegeneration, immunodeficiency, susceptibility to cancer, genomic instability, and sensitivity to ionizing radiation. Mild A-T is usually caused by ATM mutations that leave residual amounts of active ATM. This study looks at two siblings with mild A-T.

Link to Pubmed abstract
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Lung disease in ataxia-telangiectasia

Acta Paediatrica, 2007 Jul;96(7):1021-4. Epub 2007 May 24.
Bott L, Lebreton J, Thumerelle C, Cuvellier J, Deschildre A, Sardet A.

Ataxia-telangiectasia (AT) is a multi-systemic disease caused by mutational inactivation of the ATM gene. This is a retrospective study of lung disease in 15 patients. Recurrent sino-pulmonary infections are common in the first 2 years of life. Therefore early management and monitoring of lung function is necessary to minimize lung damage.

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Comparison of ataxia-telangiectasia mutated protein expression in diffuse large B-cell lymphomas of primary central nervous system and non-central nervous system origin

Archives of Pathology and Laboratory Medicine, 2007 Mar;131(3):457-67.
Kim SH, Cheong JW, Park KH, Kim TS, Yang WI.

The ataxia-telangiectasia mutated (ATM) gene encodes a nuclear 370-kd phosphoprotein known to be associated with chromosomal regions containing double-strand breaks. The mutations in the ATM gene may be involved in the development of some subtypes of sporadic lymphomas and leukemias. This study looks at the pathogenetic role of ATM mutation in the primary central nervous system diffuse large B-cell lymphomas (PCNS DLBCLs).

Link to Pubmed abstract
Link to full text

HIV-1 Vpr induces ATM-dependent cellular signal with enhanced homologous recombination.

Oncogene, 2007 Jan 25;26(4):477-86. Epub 2006 Sep 18.
Nakai-Murakami C, Shimura M, Kinomoto M, Takizawa Y, Tokunaga K, Taguchi T, Hoshino S, Miyagawa K, Sata T, Kurumizaka H, Yuo A, Ishizaka Y.

An ATM-dependent cellular signal, a DNA-damage response, has been shown to be involved during infection of human immunodeficiency virus type-1 (HIV-1), and a high incidence of malignant tumor development has been observed in HIV-1-positive patients. Vpr, an accessory gene product of HIV-1, delays the progression of the cell cycle at the G2/M phase, and ATR-Chk1-Wee-1, another DNA-damage signal, is a proposed cellular pathway responsible for the Vpr-induced cell cycle arrest. In this study, you can see evidence that Vpr also activates ATM, and induces expression of gamma-H2AX and **phosphorylation** of Chk2

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Literature on CGD

Fungal infections in primary immunodeficiencies

European Journal of Pediatrics, 2007 Nov;166(11):1099-117. Epub 2007 Jun 6.
Antachopoulos C, Walsh TJ, Roilides E.

Patients with **primary immunodeficiencies** such as chronic granulomatous disease, severe combined immunodeficiency and chronic mucocutaneous candidiasis to name a few, have an increased susceptibility to a range of fungal infections. These fungal infections may in fact be the presenting clinical manifestation of a primary immunodeficiency and can cause significant morbidity and potentially fatal outcomes if misdiagnosed or mistreated.

Link to Pubmed abstract

Liposome-Mediated Cellular Delivery of Active gp91

PLoS ONE. 2007 Sep 12;2(9):e856.
Marques B, Liguori L, Paclet MH, Villegas-Mendéz A, Rothe R, Morel F, Lenormand JL.

Gp91phox is a transmembrane protein and the catalytic core of the NADPH oxidase complex of neutrophils. Lack of this protein causes chronic granulomatous disease (CGD), a rare genetic disorder characterized by severe and recurrent infections due to the incapacity of phagocytes to kill microorganisms. In this study, the researchers assessed the potential of the cell-free expression system to synthesize functional truncated forms of the gp91phox subunit and its capacity to directly produce proteoliposomes containing these truncated forms.

Link to Pubmed abstract

Link to full article in PLOS One

A study of bone marrow transplantation in a child with chronic granulomatous disease

European Journal of Pediatrics, 2007 Aug;166(8):785-8. Epub 2006 Nov 14.
Schuetz C, Hoenig M, Schulz A, Lee-Kirsch MA, Roesler J, Friedrich W, von Bernuth H.

This case study report focuses on a 6-year-old boy with chronic granulomatous disease (CGD) complicated by chronic inflammatory reactions. A bone marrow transplantation from an unrelated donor showed favourable results.

Link to Pubmed abstract

Literature on Malnutrition

The impact of HIV on mortality during in-patient rehabilitation of severely malnourished children in Malawi.

Trans R Soc Trop Med Hyg. 2008 Jul;102(7):639-44. Epub 2008 Jun 4.
Chinkhumba J, Tomkins A, Banda T, Mkangama C, Fergusson P.

A prospective cohort study conducted in Malawi measured the mortality of HIV infected and uninfected children aged 6-59 months during nutritional rehabilitation. The children were all categorised as having severe acute malnutrition (SAM). They were followed from admission up to 4 months post discharge from the nutrition rehabilitation unit. The results showed that the mortality rates amongst the HIV infected children were significantly higher then uninfected children. Furthermore, children with CD4% <20 were almost three times more likely to die than those with a CD4% > 20. The study therefore concludes that routine testing and treatment for HIV among all malnourished children is necessary to improve quality of care and to reduce the mortality among children with SAM.

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Maternal Disease Stage and Child Undernutrition in Relation to Mortality

Among Children Born to HIV-Infected Women in Tanzania.

Journal of acquired immune deficiency syndrome, 2007 Dec 15;46(5):599-606.
Chatterjee A, Bosch RJ, Hunter DJ, Fataki MR, Msamanga GI, Fawzi WW.

This is a prospective cohort study which was conducted in Tanzania to determine if the stage of maternal HIV during pregnancy and child malnutrition is associated with child mortality.

Link to Pubmed abstract
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Micronutrients and T-cell subsets: a comparison between HIV-infected and uninfected, severely malnourished Rwandan children.

Annals of Tropical Paediatrics, 2007 Dec;27(4):269-75
Ndagije F, Baribwira C, Coulter JB.

This study looked at 112 Rwandan children aged between 2 months and 5 years who had severe malnutrition. Half of the participants were HIV positive. Tests were done to determine the levels of CD4+ cells, and the micronutrients zinc, selenium and copper. The study then compared the results to see if there was a difference of these levels in HIV- infected and uninfected malnourished children.

Link to Pubmed abstract
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Food insecurity-a risk factor for HIV infection.

PLoS Medicine, 2007 Oct 23;4(10):1576-7.
Rollins N.

There are two important links between HIV and nutrition. The first is the wasting which HIV causes, and the consequent need to determine the macro and micronutrient requirements of infected people. The second link is that of food insecurity and how poverty and concern for dependents can drive individuals into risky behaviours and then susceptibility to the disease once exposed. Little is known about this behaviour. The focus of this study is therefore on food insecurity and HIV risk behaviour.

Link to abstract
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Adverse effects of highly active antiretroviral therapy in developing countries.

Clinical Infectious Diseases, 2007 Oct 15;45(8):1093-101. Epub 2007 Sep 6.
Subbaraman R, Chaguturu SK, Mayer KH, Flanigan TP, Kumarasamy N

This study looks at the **management of drug toxicities** and adverse effects to highly active **antiretroviral therapy** (HAART) in developing countries. This is important because in these settings there is a high prevalence of conditions such as advanced HIV, anaemia, malnutrition and TB which must be considered.

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Addressing malnutrition in young children in South Africa. Setting the national context for paediatric food-based dietary guidelines.

Maternal and Child Nutrition, 2007 Oct;3(4):230-8
Bourne LT, Hendricks MK, Marais D, Eley B

Despite various national nutrition and primary healthcare programmes being initiated in South Africa over the last decade, child health has deteriorated. Evidenced by the rise in infant and child mortality rates, the high prevalence of preventable childhood diseases, and the coexistence of under-nutrition along with HIV/AIDS. This reviews the introduction of specifically targeted paediatric food based dietary guidelines for mothers and caregivers of children from birth to age 7 years, as a national initiative.

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What's new? Investigating risk factors for severe childhood malnutrition in a high HIV prevalence South African setting.

Scandinavian Journal of Public Health, 2007 Aug;69:96-106
Saloojee H, De Maayer T, Garenne ML, Kahn K.

Despite the increasing contribution of HIV to the development of severe malnutrition, traditional risk factors such as poor nutrition, parental disadvantage and illness, poverty, and social inequity remain important contributors to the prevalence of severe malnutrition. Interventions aiming to prevent and reduce severe childhood malnutrition in high HIV prevalent settings need to encompass the various

dimensions of the disease.

Link to abstract

Literature on HIV Virus

Isolated HIV-1 core is active for reverse transcription.

Retrovirology, 2007 Oct 24;4:77.
Warrilow D, Stenzel D, Harrich D.

This paper discusses the controversial question of whether purified HIV-1 virion cores are capable of reverse transcription or if they require uncoating to be activated. The researchers purified cores from a virus culture and tested for the ability to generate authentic reverse transcription products. Core-like particles were identified in this active fraction by electron microscopy.

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HIV-1 DNA Flap formation promotes uncoating of the pre-integration complex at the nuclear pore.

The EMBO Journal, 2007 Jun 20;26(12):3025-37. Epub 2007 Jun 7.
Arhel NJ, Souquere-Besse S, Munier S et al.

The HIV-1 central DNA Flap acts as a cis-acting determinant of HIV-1 genome nuclear import and DNA-Flap re-insertion in lentiviral-derived gene transfer vectors strongly stimulates gene transfer efficiencies. This study aimed to understand the mechanisms by which the central DNA Flap mediates HIV-1 nuclear import and the results show that DNA Flap formation, the very last event of HIV-1 RT degrees, acts as a viral promoting element for the uncoating of HIV-1 at the nuclear pore.

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Literature on TB Drugs

Treatment outcomes for HIV-uninfected patients with multidrug-resistant and extensively drug-resistant tuberculosis

Clinical Infectious Diseases, 2008 Aug 15;47(4):496-502.
Kwon YS, Kim YH, Suh GY, Chung MP.

This paper looks at the difficulties in successfully treating patients with multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB). The study assessed the treatment of 155 patients over a period of 9 years at a tertiary hospital in Seoul. Of these patients, 66% completed their therapy and the treatment success rates were found to be the same in patients with MDR and XDR-TB. The patients received individualized treatment with predictors of favourable outcome including a BMI >18.5, use of more than 4 effective drugs and a negative sputum result.

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Tackling tissue destruction in tuberculosis.

Transactions of the Royal Society of Tropical Medicine and Hygiene, 2008 Jul 2.
Friedland JS.

This study looks at a novel approach in the treatment of TB. To date there are limited antimicrobial drugs and no new vaccine development to counteract this worldwide problem, especially with the emergence of drug-resistant TB. The immune system controls TB until active disease develops, after which the immune response actually drives tissue destruction with enzymatic activity and matrix metalloproteinase. This study examines the use of a combination of antibiotic therapy to limit the activity of metalloproteinase and thus limit tissue damage by inhibiting enzymes and their regulatory pathways.

Link to Pubmed abstract
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Tuberculosis: vaccines in the pipeline

Expert Review of Vaccines, 2008 Jul;7(5):635-50.
Ly LH, McMurray DN.

The current TB vaccine- Mycobacterium bovis bacillus Calmette-Guerin (BCG) is widely used throughout the world, but has limited efficacy in high burden countries, especially those with the

added complication of co-infection with HIV. In the last 15 years, new strategies to improve or replace BCG have led to several promising laboratory vaccine candidates that are actively being evaluated in human clinical trials. This paper summarizes the progress of vaccine candidates in animal models to improve, replace or augment BCG vaccination

Link to PubMed abstract
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Drug lymphocyte stimulation test in the diagnosis of adverse reactions to anti-tuberculosis drugs

Chest. 2008 Jun 26.
Suzuki Y, Miwa S, Shirai M et al.

The aim of this prospective study was to evaluate the usefulness of the drug lymphocyte stimulation test (DLST) in determining anti-TB drug side effects. The study involved 436 TB infected patients taking isoniazid, rifampin, ethambutol and pyrazinamide. DLST was performed in patients who had certain adverse drug reactions during TB treatment. However, results showed that DLST offers little contribution to the detection of causative agents in patients with adverse anti-TB drug reactions.

Link to PubMed abstract

Literature on HLA

MHC class II antigen presentation and immunological abnormalities due to deficiency of MHC class II and its associated genes.

Experimental and Molecular Pathology, 2008 Aug; 85(1):40-4. Epub 2008 Apr 13
Chen X, Jensen PE

This article explains how antigen presentation by Major Histocompatibility Complex (MHC) class II molecules plays an important role in controlling immunity and autoimmunity. What has been shown is that multiple co-factors, including the invariant chain (Ii), HLA-DM and HLA-DO are involved in this process. To date the roles of Ii and DM are well understood, however, the functioning of DO has remained obscure. The data presented here indicates that DO inhibits presentation of endogenous self-antigens and that developmentally-regulated DO expression enables antigen presenting cells to preferentially present different sources of peptide antigens at different stages of development. Disruption of this regulatory mechanism results in both immunodeficiency and autoimmunity.

Link to PubMed abstract
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Genetic influence of the nonclassical major histocompatibility complex class I molecule MICB in multiple sclerosis susceptibility

Tissue Antigens, 2008 Jul;72(1):54-9
Fernandez-Morera JL, Rodriguez-Rodero S, Tunon A et al.

This study looks beyond the current knowledge that major histocompatibility complex (MHC) class II provides the main genetic contribution to multiple sclerosis (MS) to see if MHC class I is also involved in disease susceptibility. The researchers analysed the distribution of HLA-DR, HLA-B, MICB and MICA alleles in 121 MS patients and 156 healthy controls. Results showed that neither HLA-B nor MICA alleles were found to be associated with MS susceptibility. However, MICB*004 allele frequency was significantly increased in MS patients. These results are therefore strongly suggestive of MHC class I involvement in MS susceptibility.

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Human leukocyte antigen-specific polymorphisms in HIV-1 Gag and their association with viral load in chronic untreated infection

AIDS, 2008 Jul 11;22(11):1277-86
Brumme ZL, Tao I, Szeto S, Brumme CJ et al

A selection of specific human leukocyte antigen (HLA)-restricted cytotoxic T-lymphocyte (CTL) escape mutations in key Gag epitopes have been associated with loss of HIV immune control on an individual basis. In this study using a cross- sectional analysis of 567 chronically HIV infected, treatment-naïve individuals, the researchers undertook a population-based identification of HLA-associated polymorphisms in Gag and investigated their relationship with plasma viral load.

Results showed a modest inverse correlation between the total number of HLA-associated Gag polymorphic sites within each individual and plasma viral load in chronic untreated infection. This supports the hypothesis that a broad ability to target Gag in vivo contributes to viral control. Furthermore, understanding immune-driven viral adaptation has implications for HIV vaccine development.

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Assessing vaccine potency using TCRmimic antibodies

Vaccine. 2008 Jun 13;26(25):3092-102. Epub 2008 Feb 25.
Neethling FA, Ramakrishna V, Keler T, Buchli R, Woodburn T, Weidanz JA.

Dendritic cells (DCs) are highly specialised antigen-presenting cells (APCs) of the immune system which are efficient at presenting peptide-antigen for the activation of T cells. Because of their high expression levels of MHC and costimulatory molecules, these are often the cell type of choice for vaccine targeting. In this study, the researchers first generated antibodies (TCR mimics or TCRm) to two peptide-HLA-A*0201 epitopes derived from hCGβ designated as TMT (40–48) and GVL (47–55). Characterisation of each TCRm by ELISA and flow cytometric analysis, demonstrated specific binding to soluble recombinant HLA-A2 protein and HLA-A2.1+ T2 cells loaded with relevant peptide. Results demonstrated that TCRms may be important tools for determining the potency of DC-based vaccines.

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T cell receptor engagement of peptide-major histocompatibility complex class I does not modify CD8 binding

Mol Immunol. 2008 May;45(9):2700-9. Epub 2008 Feb 19.
Cole DK, Dunn SM, Sami M, Boulter JM, Jakobsen BK, Sewell AK.

Activation of cytotoxic T cells is initiated by engagement of the T-cell receptor (TCR) with peptide-major histocompatibility class I complexes (MHCI). The CD8 co-receptor also binds to MHCI, but at a distinct site, and allows the potential for tripartite TCR/MHCI/CD8 interactions, which can increase T cell antigen sensitivity. This study uses enhanced TCRs, which have extended off-rates of approximately 1h compared to seconds for the wildtype TCRs, to examine pMHCI/CD8 binding before and during TCR-engagement. The study shows that the binding of the extracellular domain of the TCR to MHCI does not transmit structural changes to the MHCI-CD8 binding site that would alter the subsequent MHCI/CD8 interaction.

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Literature on Hyper IgM Syndrome

Cellular and Molecular Characterisation of the Hyper Immunoglobulin M Syndrome Associated with Congenital Rubella Infection.

J Clin Immunol. 2008 Jul 29
Ameratunga R, Woon ST, Koopmans W, French J.

In this study of a 53 year old male with hyper-immunoglobulin M syndrome (HIM), revealed no mutations in the CD40 ligand while T-cell responses to lectins and antigens were normal. His B-cell proliferation, isotype switching and production of memory B cells are also normal. However, his CD40/IL4 dependent rescue from anti-IgM-induced apoptosis is impaired, which concludes that the detection of cell-surface IgG but lack of serum IgG indicates that he may have an antibody secretion defect.

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Severe Congenital Neutropenia or Hyper-IgM Syndrome? A Novel Mutation of CD40 Ligand in a Patient with Severe Neutropenia

Arch Allergy Immunol. 2008 Jul 2;147(3):255-259.
Rezaei N, Aghamohammadi A, Ramyar A, Pan-Hammarstrom Q, Hammarstrom L. Int

This study shows that two primary **immunodeficiency diseases** caused by different underlying genetic defects can present in similar ways. The two conditions of interest are severe congenital neutropenia (SCN) and CD40 ligand deficiency (CD40LD). The patient discussed is a 3 year old boy who presented with signs and symptoms including a severe consistent neutropenia and maturation arrest in the myeloid series in the bone marrow. On presentation he was diagnosed with SCN.

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Autoimmunity in hyper-IgM syndrome

J Clin Immunol. 2008 May;28 Suppl 1:S62-6. Epub 2008 Feb 2.
Jesus AA, Duarte AJ, Oliveira JB.

This article reviews the main subtypes of hyper-IgM (HIGM) syndrome, the clinical autoimmune manifestations found in these patients, and the possible mechanisms that would explain this association. Immunodeficiency with HIGM results from genetic defects in the CD40-CD40 ligand

(CD40L) pathway or in the enzymes required for immunoglobulin class switch recombination and somatic hypermutation. HIGM can thus be associated with an impairment of both B-cell and T-cell activation. There are seven main subtypes of HIGM, the most frequent is X-linked HIGM, resulting from CD40L mutations. In addition to the susceptibility to recurrent and opportunistic infections, these patients are prone to autoimmune manifestations, especially hematologic abnormalities, arthritis, and inflammatory bowel disease.

Link to PubMed abstract
Link to full text

Molecular analysis of a large cohort of patients with the hyper immunoglobulin M (IgM) syndrome.

Blood. 2005 Mar 1;105(5):1881-90. Epub 2004 Sep 9
Lee WI, Torgerson TR, Schumacher MJ et al.

This study investigated the molecular basis of hyper immunoglobulin M (IgM) syndrome HIGM, by looking at 5 molecular defects which included mutations of the genes coding for CD40 ligand and IKK-gamma. The syndrome is characterised by recurrent infections, low serum IgG and IgA while IgM levels remain normal or elevated and defective class switching. Of the 140 patients tested CD40 ligand mutations were found in the largest group made up of 98 male participants.

Link to PubMed abstract
Link to full text

The Hyper IgM syndrome.

Curr Allergy Asthma Rep. 2001 Sep;1(5):445-50.
Fuleihan RL.

There are two types of the rare hyper IgM syndrome, which results from defects in the CD40 ligand/CD40- signaling pathway. The first type is X-linked hyper IgM and is caused by defects in the CD40 ligand gene, while autosomal recessive hyper IgM is caused by defects in the CD40-activated RNA-editing enzyme, activation-induced cytidine deaminase, which is required for immunoglobulin isotype switching and somatic hypermutation in B cells. With genetic defects in the hyper IgM syndrome identified, it is possible to diagnose patients, to perform genetic screening, and to delineate the clinical manifestations of this syndrome.

Link to PubMed abstract

Mutations in activation-induced cytidine deaminase in patients with hyper IgM syndrome.

Clin Immunol. 2000 Dec;97(3):191-2.
Minegishi Y, Lavoie A, Cunningham-Rundles C et al

Recent studies have shown that mutations in a newly described RNA editing enzyme, activation-induced cytidine deaminase (AID), can cause an autosomal recessive form of hyper IgM syndrome. To determine the relative frequency of mutations in AID, the study evaluated a group of 27 patients with hyper IgM syndrome who did not have defects in CD40 ligand and 23 patients with common variable immunodeficiency. Three different mutations in AID were identified in 18 patients with hyper IgM syndrome. No mutations were found in the remaining 32 patients. In the group of patients with hyper IgM syndrome, the patients with mutations in AID were older at the age of diagnosis, were more likely to have positive isohemagglutinins, and were less likely to have anemia, neutropenia, or thrombocytopenia.

Link to PubMed abstract
Link to full text

Literature on Inflammatory Bowel Disease

High frequency of early colorectal cancer in inflammatory bowel disease

Gut. 2008 Sep;57(9):1246-51. Epub 2008 Mar 12
Lutgens MW, Vleggaar FP, Schipper ME, et al.

The current guidelines for colonoscopic surveillance for precancerous dysplasia in patients with inflammatory bowel disease (IBD) is 8-10 years for extensive colitis or 15-20 years for left sided disease. This study conducted in seven medical centres in The Netherlands aimed to assess the time interval between onset of (IBD) and colorectal carcinoma (CRC), and how many patients developed cancer before the recommended surveillance time. The results showed that the diagnosis of colorectal cancer was delayed or missed in a substantial number of patients (17-28%) when conducting surveillance strictly according to formal guidelines.

Link to PubMed article
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Basal lymphoid aggregates in ulcerative colitis colon: a site for regulatory T cell action.

Clin Exp Immunol. 2008 Feb;151(2):326-33
Sitohy B, Hammarström S, Danielsson A, Hammarström ML.

It has been suggested that immune tolerance in the gut mucosa is maintained by regulatory T cells, and in ulcerative colitis (UC) patients' regulatory T cells appear to produce high levels of interleukin (IL)-10 in the inflamed colonic tissue. This study attempts to determine whether the frequency of regulatory T cells is increased in UC colon and whether they are present in the basal lymphoid aggregates.

Colonic tissue specimens from UC and control patients were analysed for frequencies of lamina propria lymphocytes expressing the regulatory T cell markers forkhead box protein 3 (FoxP3), CD25 and glucocorticoid-induced tumour necrosis factor (GITR). The results showed that GITR+ and FoxP3+ cells were present in normal colon mucosa, although at a relatively low frequency, and were located preferentially within the solitary follicles. Whereas UC affected colon was associated with significantly increased frequencies of CD25+, GITR+ and FoxP3+ lamina propria lymphocytes both within the basal lymphoid aggregates and in the lamina propria outside. However, increased frequency of regulatory T cell subtypes appeared to be insufficient to control the disease activity in UC.

Link to PubMed Article
Link to full article

Literature on Ankylosing spondylitis

Literature on Acute Retroviral Syndrome

The efficacy of T cell-mediated immune responses is reduced by the envelope protein of the chimeric HIV-1/SIV-KB9 virus in vivo

Journal of Immunology, 2008 Oct 15;181(8):5510-21.
Stevceva L, Yoon V, Carville A, et al.

Gp120 is one of the main proteins found in the HIV-1 envelope and plays an important role in viral entry. Due to its location in the envelope it is the part of the virus that immune cells encounter first and therefore has the ability to influence immune responses. Based on this fact, this study has looked at how high levels of gp120 can contribute to the failure of the immune system by contributing to virus survival and persistence because it is unable to control and clear the virus.

Link to Pubmed abstract

The dual role of dendritic cells in the immune response to human immunodeficiency virus type 1 infection

Journal of General Virology, 2008 Sep;89(Pt 9):2228-39
Hogue IB, Bajaria SH, Fallert BA, Qin S, Reinhart TA, Kirschner DE.

This study looks at the complex interactions between HIV-1 and the immune system, with the main focus on the role of dendritic cells. These cells have a dual role of enhancing the infection process and promoting the immune response. In this study the role of dendritic cells, HIV-1, CD4+ and CD8+ T-cells were described in a mathematical model. The model qualitatively and quantitatively recapitulated clinical HIV-1 infection dynamics performing sensitivity analyses to determine which mechanisms strongly affect infection dynamics. The model predicted that, while direct failure of dendritic cell function and indirect failure due to loss of CD4+ T-helper cells were both significant contributors to infection dynamics, the former showed a more significant impact on HIV-1 pathogenesis.

Link to Pubmed Abstract

Literature on Ulcerative Colitis

Extraintestinal manifestations of inflammatory bowel disease

Current Gastroenterology Reports. 2008 Dec;10(6):597-605
Williams H, Walker D, Orchard TR

Crohn's disease and ulcerative colitis are complicated by extraintestinal manifestations (EIMs) in up to 40% of people with one or other or the conditions, also know as inflammatory bowel disease (IBD). Although all organ systems may be affected, EIMs occur in a large proportion of cases and are a source of distress for patients. Based on the influence of genetic factors in the pathogenicity of the condition, attempts have been made to define the phenotype of IBD in patients of different ethnicities. What was found is that some of the EIMs are related to the disease while others have been found to run a course independent of the disease and therefore require different management.

Link to Pubmed abstract