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# Selected published abstracts of Baylor researchers

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## ARCHIVES OF DERMATOLOGY

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### **Efficacy and safety observed during 24 weeks of efalizumab therapy in patients with moderate to severe plaque psoriasis**

Menter A, Gordon K, Carey W, Hamilton T, Glazer S, Caro I, Li N, Gulliver W; Efalizumab Study Group

(*Arch Dermatol* 2005;141:31–38) Copyright © 2005, American Medical Association. All rights reserved.

**Objective:** To assess the efficacy and safety of a 24-week course of efalizumab.

**Design:** Phase 3, randomized, double-blind, parallel-group, placebo-controlled 12-week study followed by a 12-week open-label study.

**Setting:** Outpatient dermatology clinics.

**Patients:** A total of 556 patients with moderate to severe chronic plaque psoriasis who were seeing an outpatient dermatologist were included in the study.

**Intervention:** For weeks 1 to 12, the 556 patients were randomized to receive 1 mg/kg of efalizumab weekly or placebo subcutaneously. For weeks 13 to 24, 516 of these patients received 1 mg/kg of efalizumab weekly.

**Main outcome measures:** Proportion of patients with a 75% or greater improvement in Psoriasis Area and Severity Index (PASI-75), a 50% or greater improvement in PASI (PASI-50), static Physician's Global Assessment (sPGA) rating of minimal or clear, and improvements in Dermatology Life Quality Index (DLQI), itching scale, and Psoriasis Symptom Assessment (PSA) frequency and severity scores at weeks 12 and 24. Safety was evaluated by reviewing adverse events, laboratory parameters, vital signs, and anti-efalizumab antibodies.

**Results:** At week 12, 26.6% of efalizumab-treated patients achieved PASI-75 and 58.5% achieved PASI-50. After 24 weeks of continuous efalizumab therapy, PASI responses increased: 43.8% of patients achieved PASI-75 and 66.6% achieved PASI-50. The percentage of patients who achieved an sPGA rating of minimal or clear increased from 25.7% to 35.9%. The mean percentage of improvement in all patient-reported outcomes (DLQI, itching scale, and PSA frequency and severity scores) at week 12 was maintained at week 24 (DLQI, 49.2%; itching scale, 42.2%; PSA frequency, 47.6%; PSA severity, 47.3%). There was a decline in overall reported adverse events from weeks 1 to 12 (80.4%) to weeks 13 to 24 (63.2%) without evidence of cumulative toxic effects.

**Conclusion:** Extending efalizumab treatment from 12 to 24 weeks leads to improved efficacy and maintenance of quality of life with no evidence of cumulative toxic effects noted in patients with moderate to severe chronic plaque psoriasis.

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## CIRCULATION

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### **Frequency by decades of unicuspid, bicuspid, and tricuspid aortic valves in adults having isolated aortic valve replacement for aortic stenosis, with or without associated aortic regurgitation**

Roberts WC, Ko JM

(*Circulation* 2005;111:920–925. Related editorial in 111:832–834.)

**Background:** Aortic valve stenosis (with or without aortic regurgitation and without associated mitral stenosis) in adults in the Western world

has been considered in recent years to most commonly be the result of degenerative or atherosclerotic disease.

**Methods and results:** We examined operatively excised, stenotic aortic valves from 932 patients aged 26 to 91 years (mean  $\pm$  SD, 70  $\pm$  12), and none had associated mitral valve replacement or evidence of mitral stenosis: A total of 504 (54%) had congenitally malformed valves (unicuspid in 46 [unicommissural in 42; acommisural in 4] and bicuspid in 458); 417 (45%) had tricuspid valves (either absent or minimal commissural fusion); and 11 (1%) had valves of undetermined type. It is likely that the latter 11 valves also had been congenitally malformed. Of the 584 men, 343 (59%) had either a unicuspid or a bicuspid valve; of the 348 women, 161 (46%) had either a unicuspid or a bicuspid aortic valve.

**Conclusions:** The data from this large study of adults having isolated aortic valve replacement for aortic stenosis (with or without associated aortic regurgitation) and without associated mitral stenosis or mitral valve replacement strongly suggest that an underlying congenitally malformed valve, at least in men, is more common than a tricuspid aortic valve.

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## CLINICAL BREAST CANCER

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### **Feasibility of quantifying the effects of epoetin alfa therapy on cognitive function in women with breast cancer undergoing adjuvant or neoadjuvant chemotherapy**

O'Shaughnessy JA, Vukelja SJ, Holmes FA, Savin M, Jones M, Royall D, George M, Hoff DV

(*Clin Breast Cancer* 2005;5:439–446) Reprinted with permission from Cancer Information Group.

Impaired cognition, fatigue, and diminished quality of life (QOL) are commonly associated with breast cancer chemotherapy. This randomized, double-blind, placebo-controlled pilot trial assessed the feasibility of quantifying the effects of epoetin alfa on cognitive function and mood, and evaluated its effects on fatigue and QOL in patients with breast cancer treated with anthracycline-based adjuvant or neoadjuvant chemotherapy. Patients were randomized to receive epoetin alfa 40,000 U subcutaneously once weekly or placebo at the beginning of 4 cycles of chemotherapy administered over 12 weeks. Cognitive function was assessed by Executive Interview (EXIT25) and Clock Drawing Tasks; mood by Profile of Mood States; anemia-related symptoms, including fatigue, by the Functional Assessment of Cancer Therapy–Anemia (FACT-An) subscale; and QOL by Linear Analog Scale Assessment. Ninety-four patients were evaluable for efficacy and safety. Mean change in EXIT25 scores from baseline to cycle 4 in the epoetin alfa group was  $-1.3 \pm 3.3$ ; the mean change was  $0.3 \pm 2.4$  in the placebo group (a negative change indicates improved executive function). There was no difference between groups in mean change in EXIT25 score from baseline to 6-month follow-up assessment. Mean hemoglobin levels were higher in the epoetin alfa group compared with the placebo group after 4 cycles of chemotherapy. Epoetin alfa recipients had less of a decrease in FACT-An subscale scores from baseline to cycle 4 and improvement in FACT-An subscale scores at 6-month follow-up assessment compared with placebo. Epoetin alfa therapy was well tolerated. These data suggest that epoetin alfa may have attenuated the cognitive impairment and fatigue that occurred during adjuvant breast cancer chemotherapy.

**Increased blood myeloid dendritic cells and dendritic cell-poietins in Langerhans cell histiocytosis**

Rolland A, Guyon L, Gill M, Cai YH, Banchemareau J, McClain K, Palucka AK

*(J Immunol 2005;174:3067–3071) Copyright 2005. The American Association of Immunologists, Inc.*

Langerhans cell histiocytosis (LCH), previously known as histiocytosis X, is a reactive proliferative disease of unknown pathogenesis. Current therapies are based on nonspecific immunosuppression. Because multiple APCs, including Langerhans cells and macrophages, are involved in the lesion formation, we surmised that LCH is a disease of myeloid blood precursors. We found that  $\text{lin}^- \text{HLA-DR}^+ \text{CD11c}^+$  precursors of dendritic cells, able to give rise to either Langerhans cells or macrophages, are significantly ( $P = 0.004$ ) increased in the blood of LCH patients. The analysis of serum cytokines in 24 patients demonstrated significantly elevated levels of hemopoietic cytokines such as  $\text{fms-like tyrosine kinase ligand (FLT3-L, a dendritic cell-mobilizing factor, } \sim 2\text{-fold)}$  and  $\text{M-CSF (} \sim 4\text{-fold)}$ . Higher levels of these cytokines correlated with patients having more extensive disease. Serum levels of FLT3-L and M-CSF were highest in high-risk patients with extensive skin and/or multisystem involvement. Finally, patients with bone lesions had relatively higher levels of M-CSF and of stem cell factor. Thus, early hemopoietic cytokines such as FLT3-L, stem cell factor, and M-CSF may be relevant in LCH pathogenesis and might be considered as novel therapeutic targets.

**IFN- $\alpha$  induces early lethal lupus in preautoimmune (New Zealand Black  $\times$  New Zealand White) $F_1$  but not in BALB/c mice**

Mathian A, Weinberg A, Gallegos M, Banchemareau J, Koutouzov S

*(J Immunol 2005;174:2499–2506) Copyright 2005. The American Association of Immunologists, Inc.*

Recent studies indicate that IFN- $\alpha$  is involved in pathogenesis of systemic lupus erythematosus. However, direct proof that IFN- $\alpha$  is not only necessary, but also sufficient to induce lupus pathogenicity is lacking. In this study, we show that *in vivo* adenovector-mediated delivery of murine IFN- $\alpha$  results in preautoimmune (New Zealand Black (NZB)  $\times$  New Zealand White (NZW)) $F_1$ , but not in normal, mice, in a rapid and severe disease with all characteristics of systemic lupus erythematosus. Anti-dsDNA Abs appeared as soon as day 10 after initiation of IFN- $\alpha$  treatment. Proteinuria and death caused by glomerulonephritis occurred in all treated mice within, respectively,  $\sim 9$  and  $\sim 18$  wk, at a time when all untreated (NZB  $\times$  NZW) $F_1$  did not show any sign of disease. IFN- $\alpha$  *in vivo* induced an overexpression of B lymphocyte stimulator in circulation at similar levels in both the preautoimmune and the normal mouse strains. All effects elicited by IFN- $\alpha$  were dose dependent. (NZB  $\times$  NZW) $F_1$  infused with purified murine IFN- $\alpha$  also showed acceleration of lupus. Thus, prolonged expression of IFN- $\alpha$  *in vivo* induces early lethal lupus in susceptible animals.

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**JOURNAL OF IMMUNOTHERAPY**

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**Measuring melanoma-specific cytotoxic T lymphocytes elicited by dendritic cell vaccines with a tumor inhibition assay *in vitro***

Paczesny S, Shi H, Saito H, Mannoni P, Fay J, Banchemareau J, Palucka AK

*(J Immunother 2005;28:148–157)*

Improving cancer vaccines depends on assays measuring elicited tumor-specific T-cell immunity. Cytotoxic effector cells are essential for tumor clearance and are commonly evaluated using  $^{51}\text{Cr}$  release from labeled

target cells after a short (4 hours) incubation with T cells. The authors used a tumor inhibition assay (TIA) that assesses the capacity of cytotoxic T lymphocytes (CTLs) to control the survival/growth of EGFP-labeled tumor cell lines. TIA was validated using  $\text{CD8}^+$  T cells primed *in vitro* against melanoma and breast cancer cells. TIA was then used to assess the CTL function of cultured  $\text{CD8}^+$  T cells isolated from patients with metastatic melanoma who underwent vaccination with peptide-pulsed  $\text{CD34}^+$  HPCs-derived DCs. After the DC vaccination, T cells from six of eight patients yielded CTLs that could inhibit the survival/growth of melanoma cells. The results of TIA correlated with killing of tumor cells in a standard 4-hour  $^{51}\text{Cr}$  release assay, yet TIA allowed detection of CTL activities that appeared marginal in the  $^{51}\text{Cr}$  release assay. Thus, TIA might prove valuable for measuring spontaneous and induced antigen-specific cytotoxic T cells.

**Boosting vaccinations with peptide-pulsed  $\text{CD34}^+$  progenitor-derived dendritic cells can expand long-lived melanoma peptide-specific  $\text{CD8}^+$  T cells in patients with metastatic melanoma**

Palucka AK, Dhodapkar MV, Paczesny S, Ueno H, Fay J, Banchemareau J

*(J Immunother 2005;28:158–168)*

The immunogenicity of dendritic cell (DC)-based vaccines has been shown in patients with advanced cancer, but it has not yet been established whether the elicited cancer-specific immunity is durable and whether it can be maintained by boosting vaccinations. The authors showed earlier, in 18 HLA-A\*0201 metastatic melanoma patients, that four vaccinations over 6 weeks with peptide-loaded  $\text{CD34-DCs}$  (the induction phase) expand in the blood melanoma-specific  $\text{CD8}^+$  T cells, as documented by melanoma peptide-specific IFN- $\gamma$  ELISPOT and cytotoxic T-lymphocyte (CTL) activity against melanoma cell lines. The authors show here that the melanoma peptide-specific  $\text{CD8}^+$  T-cell immunity is short-lived, but it could be reactivated in 7 of 11 patients who received four boosting vaccinations with peptide-loaded  $\text{CD34-DCs}$ . Expansion of recall memory  $\text{CD8}^+$  T cells was confirmed by tetramer binding and CTL activity against melanoma peptide-pulsed T2 cells. In two patients boosted over 15 months, induced melanoma peptide-specific recall memory  $\text{CD8}^+$  T cells lasted at least 6 months. Thus, boosting vaccination with peptide-loaded  $\text{CD34-DCs}$  can expand long-lived tumor peptide-specific immunity.

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**JOURNAL OF INFECTIOUS DISEASES**

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**Mobilization of plasmacytoid and myeloid dendritic cells to mucosal sites in children with respiratory syncytial virus and other viral respiratory infections**

Gill MA, Palucka AK, Barton T, Ghaffar F, Jafri H, Banchemareau J, Ramilo O

*(J Infect Dis 2005;191:1105–1115)*

**Background:** Respiratory syncytial virus (RSV) is the principal etiologic agent of bronchiolitis and viral pneumonia in infants and young children. Yet, many aspects of its immunopathogenesis are not well understood.

**Methods:** We analyzed the immune cells that are mobilized by RSV and other respiratory viruses, by studying nasal wash samples from children hospitalized with acute viral respiratory infections.

**Results:** RSV mobilizes virtually all blood immune cells, including myeloid dendritic cells (DCs) and plasmacytoid DCs (pDCs), to the nasal mucosa. DCs were also mobilized to the nasal mucosa of children with other viral respiratory infections. The increased number of pDCs in the nasal compartment significantly correlates with RSV load ( $P = .022$ ), and it is associated with a significant decrease in the number of pDCs in the blood ( $P = .007$ ). The influx of DCs in the nasal mucosa is not transient,

as even higher numbers of both DC subsets were found in respiratory secretions weeks after the acute symptoms of RSV infection had resolved. Immunochemistry analysis of respiratory samples has demonstrated the presence of the RSV fusion protein within HLA-DR-positive cells.

**Conclusion:** Infection with RSV and other respiratory viruses mobilizes DCs to the site of viral entry.

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## MEDICAL CLINICS OF NORTH AMERICA

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### Surveillance of patients at high risk for colorectal cancer

Syngal S, Bandipalliam P, Boland CR

(*Med Clin North Am* 2005;89:61–84) Reprinted with permission from Elsevier.

Colorectal cancer (CRC) mortality may be greatly reduced by clinically feasible screening programs. The benefits of surveillance of high-risk programs are evident. Cancer mortality can be dramatically reduced by eradication of precursor lesions and by detection of cancer at an early and highly curable stage. Available screening methods, recommended intervals, and screening for other associated cancers are reviewed for specific high-risk groups.

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## MOLECULAR THERAPY

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### Intratumoral injection of INGN 241, a nonreplicating adenovector expressing the melanoma-differentiation associated gene-7 (*mda-7/IL24*): biologic outcome in advanced cancer patients

Tong AW, Nemunaitis J, Su D, Zhang Y, Cunningham C, Senzer N, Netto G, Rich D, Mhashilkar A, Parker K, Coffee K, Ramesh R, Ekmekcioglu S, Grimm EA, van Wart Hood J, Merritt J, Chada S

(*Mol Ther* 2005;11:160–172) Reprinted with permission of Elsevier.

The *mda-7* gene (approved gene symbol IL24) is a novel tumor suppressor gene with tumor-apoptotic and immune-activating properties. We completed a Phase I dose-escalation clinical trial, in which a nonreplicating adenoviral construct expressing the *mda-7* transgene (INGN 241; Ad-*mda7*) was administered intratumorally to 22 patients with advanced cancer. Excised tumors were evaluated for vector-specific DNA and RNA, transgenic MDA-7 expression, and biological effects. Successful gene transfer as assessed by DNA- and RT-PCR was demonstrated in 100% of patients evaluated. DNA analyses demonstrated a dose-dependent penetration of INGN 241 (up to  $4 \times 10^8$  copies/ $\mu$ g DNA at the  $2 \times 10^{12}$  vp dose). A parallel distribution of vector DNA, vector RNA, MDA-7 protein expression, and apoptosis induction was observed in all tumors, with signals decreasing with distance away from the injection site. Additional evidence for bioactivity of INGN 241 was illustrated via regulation of the MDA-7 target genes  $\beta$ -catenin, iNOS, and CD31. Transient increases (up to 20-fold) of serum IL-6, IL-10, and TNF- $\alpha$  were observed. Significantly higher elevations of IL-6 and TNF- $\alpha$  were observed in patients who responded clinically to INGN 241. Patients also showed marked increases of CD3<sup>+</sup>CD8<sup>+</sup> T cells post-treatment, suggesting that INGN 241 increased systemic T<sub>H</sub>1 cytokine production and mobilized CD8<sup>+</sup> T cells. Intratumoral delivery of INGN 241 induced apoptosis in a large volume of tumor and elicited tumor-regulatory and immune-activating events that are consistent with the preclinical features of MDA-7/IL-24.

### Fighting cancer with vaccinia virus: teaching new tricks to an old dog

Shen Y, Nemunaitis J

(*Mol Ther* 2005;11:180–195) Reprinted with permission of Elsevier.

Vaccinia virus has played a huge part in human beings' victory over smallpox. With smallpox being eradicated and large-scale vaccination stopped worldwide, vaccinia has assumed a new role in our fight against another serious threat to human health: cancer. Recent advances in molecular biology, virology, immunology, and cancer genetics have led to the design of novel cancer therapeutics based on vaccinia virus backbones. With the ability to infect efficiently a wide range of host cells, a genome that can accommodate large DNA inserts and express multiple genes, high immunogenicity, and cytoplasmic replication without the possibility of chromosomal integration, vaccinia virus has become the platform of many exploratory approaches to treat cancer. Vaccinia virus has been used as (1) a delivery vehicle for anti-cancer transgenes, (2) a vaccine carrier for tumor-associated antigens and immunoregulatory molecules in cancer immunotherapy, and (3) an oncolytic agent that selectively replicates in and lyses cancer cells.

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## NEW ENGLAND JOURNAL OF MEDICINE

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### Transmission of rabies virus from an organ donor to four transplant recipients

Srinivasan A, Burton EC, Kuehnert MJ, Rupprecht C, Sutker WL, Ksiazek TG, Paddock CD, Guarner J, Shieh WJ, Goldsmith C, Hanlon CA, Zoretic J, Fischbach B, Niezgodka M, El-Feky WH, Orciari L, Sanchez EQ, Likos A, Klintmalm GB, Cardo D, LeDuc J, Chamberland ME, Jernigan DB, Zaki SR; for the Rabies in Transplant Recipients Investigation Team

(*N Engl J Med* 2005;352:1103–1111) Copyright © 2005 Massachusetts Medical Society. All rights reserved.

**Background:** In 2004, four recipients of kidneys, a liver, and an arterial segment from a common organ donor died of encephalitis of an unknown cause.

**Methods:** We reviewed the medical records of the organ donor and the recipients. Blood, cerebrospinal fluid, and tissues from the recipients were tested with a variety of assays and pathological stains for numerous causes of encephalitis. Samples from the recipients were also inoculated into mice.

**Results:** The organ donor had been healthy before having a subarachnoid hemorrhage that led to his death. Encephalitis developed in all four recipients within 30 days after transplantation and was accompanied by rapid neurologic deterioration characterized by agitated delirium, seizures, respiratory failure, and coma. They died an average of 13 days after the onset of neurologic symptoms. Mice inoculated with samples from the affected patients became ill seven to eight days later, and electron microscopy of central nervous system (CNS) tissue demonstrated rhabdovirus particles. Rabies-specific immunohistochemical and direct fluorescence antibody staining demonstrated rabies virus in multiple tissues from all recipients. Cytoplasmic inclusions consistent with Negri bodies were seen in CNS tissue from all recipients. Antibodies against rabies virus were present in three of the four recipients and the donor. The donor had told others of being bitten by a bat.

**Conclusions:** This report documenting the transmission of rabies virus from an organ donor to multiple recipients underscores the challenges of preventing and detecting transmission of unusual pathogens through transplantation.

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## OBSTETRICAL AND GYNECOLOGICAL SURVEY

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### Resident attrition: is gender a factor?

Moschos E, Beyer MJ

(*Obstet Gynecol Surv* 2005;60:28–29)

This study was conducted to investigate the differences in resident attrition between male and female residents in obstetrics and gynecology. Two different questionnaires were sent, one in March 2001 and one in May 2002, to the residency directors or coordinators of the 246 accredited residency programs in obstetrics and gynecology in the United States. In the first mailing, questions were asked about the numbers of residents who left the program between 1997 and 2001, the postgraduate year upon leaving, their gender, and their reasons for leaving. The categories of reasons for leaving were involuntary dismissal, change of specialty, family (most often spousal) issues, change to another obstetrics and gynecology program, and miscellaneous factors. In addition to these questions, the second questionnaire asked for demographic information about the program, and the distribution of male and female residents in each year. In March 2001, 46% of the questionnaires were completed and returned (113 of 246). Twenty-two of the responding programs (21%) had not lost any residents between 1997 and 2001. The remaining programs reported losing 167 residents over the 4-year period (3.6% attrition rate). Seventy-four percent (124) of those who left the program were women compared with 25% (43) who were men ( $P = 0.029$ ). Over half (60%) of those who dropped out of a residency program left at the end of the first year. These percentages were similar for men and women. Nearly half of female residents (48%), but only one fourth of male residents (25%), left their residency for family reasons ( $P = 0.012$ ). Conversely, 55% of men and 26% of women left for a change of specialty ( $P = 0.001$ ). Equal numbers of men and women were involuntarily dismissed from their program (15% and 17%, respectively) or changed to another obstetrics and gynecology residency (5% each). Analysis of the data acquired in the first questionnaire found that women were more than twice as likely as men to leave a residency for family reasons (odds ratio [OR], 2.64; 95% confidence interval [CI], 1.22–5.70). Women were significantly less likely to leave a residency in obstetrics and gynecology for another specialty (OR, 0.275; 95% CI, 0.13–0.56). The response rate was lower for the second questionnaire (30%, 74 of 246), but the responses were similar to the first mailing. Sixteen percent of programs reported no losses, and 84% reported losing 138 residents of whom one third were men and two thirds were women (difference not significant). The attrition rate in May was 2.7%. Family considerations were cited by 52% of female residents and only 17% of male residents as the reason for leaving their training program ( $P = 0.002$ ; OR, 5.16; 95% CI, 1.71–15.60). Change of specialty was the reason for leaving in 24% of female residents compared with 50% of male residents ( $P = 0.002$ ; OR, 0.31; 95% CI, 0.12–0.80). The percentages of men and women who were involuntarily dismissed from their program or who changed to another obstetrics and gynecology program were similar.

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## PERFUSION

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### Clinical benefits of continuous leukocyte filtration during cardiopulmonary bypass in patients undergoing valvular repair or replacement

Sutton SW, Patel AN, Chase VA, Schmidt LA, Hunley EK, Yancey LW, Hebler RF, Cheung EH, Henry AC III, Meyers TP, Wood RE

(*Perfusion* 2005;20:21–29) Copyright 2005 Edward Arnold (Publishers) Ltd.

Valve operations in the form of repair or replacement make up a significant population of patients undergoing surgical procedures in the USA

annually with the use of cardiopulmonary bypass. These patients experience a wide range of complications that are considered to be mediated by activation of complement and leukocytes. The extracorporeal perfusion circuit consists of multiple synthetic artificial surfaces. The biocompatibility of the blood contact surfaces is a variable that predisposes patients to an increased risk of complement mediation and activation. This can result in an inflammatory process, causing leukocytes to proliferate and sequester in the major organ systems. The purpose of this study was to determine whether filtration of activated leukocytes improved clinical outcomes following surgical intervention for valve repair or replacement. In this paper, we report a retrospective matched cohort study of 700 patients who underwent valve procedures from June 1999 to December 2002. The control group (CG) consisted of patients who had a conventional arterial line filter. In the study group (SG), patients had a conventional arterial line filter and a leukocyte arterial line filter (Pall Medical, NY). In the SG, blood diverted to the cardioplegia system was also leukocyte depleted to enhance myocardial preservation by adapting this device to the outflow port on the filter. Patient characteristics were similar for the SG and the CG, including 228 males and 122 females, mean age (62.4 versus 64.2 years), cardiopulmonary bypass time ( $127 \pm 64$  versus  $116 \pm 53$  min), and aortic crossclamp time ( $84 \pm 23$  versus  $81 \pm 23$  min). Our results demonstrate that the SG achieved statistically significant reduction in the time to extubation ( $P = 0.03$ ) and the number of patients with prolonged intubation in excess of 24 hours ( $P < 0.04$ ), in addition to improved postoperative oxygenation ( $P = 0.01$ ), and decreased length of hospital stay ( $P = 0.03$ ). We believe that leukocyte filters are clinically beneficial, as demonstrated by the results presented in this study.

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## PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE USA

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### Cross-regulation of TNF and IFN- $\alpha$ in autoimmune diseases

Palucka AK, Blanck JP, Bennett L, Pascual V, Banchereau J

(*Proc Natl Acad Sci U S A* 2005;102:3372–3377) Copyright 2005 National Academy of Sciences, USA.

Cytokines, most particularly TNF and type I IFN (IFN- $\alpha$ ), have been long considered essential elements in the development of autoimmunity. Identification of TNF in the pathogenesis of rheumatoid arthritis and TNF antagonist therapy represent successes of immunology. IFN- $\alpha$  plays a major role in systemic lupus erythematosus (SLE), a prototype autoimmune disease characterized by a break of tolerance to nuclear components. Here, we show that TNF regulates IFN- $\alpha$  production in vitro at two levels. First, it inhibits the generation of plasmacytoid dendritic cells (pDCs), a major producer of IFN- $\alpha$ , from CD34<sup>+</sup> hematopoietic progenitors. Second, it inhibits IFN- $\alpha$  release by immature pDCs exposed to influenza virus. Neutralization of endogenous TNF sustains IFN- $\alpha$  secretion by pDCs. These findings are clinically relevant, as five of five patients with systemic juvenile arthritis treated with TNF antagonists display overexpression of IFN- $\alpha$ -regulated genes in their blood leukocytes. These results, therefore, might provide a mechanistic explanation for the development of anti-dsDNA antibodies and lupus-like syndrome in patients undergoing anti-TNF therapy.

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