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Science Transforming Life®

Selected Technologies
Technology Transfer Office

National Jewish Health, in Denver, Colorado, is a world-renowned respiratory, medical and research institution with a 115-year heritage of making groundbreaking discoveries and providing revolutionary treatments.

National Jewish Health collaborates with pharmaceutical and biotechnology companies to develop therapeutic and diagnostic products, as well as supports the commercialization of our industry partners' products.

The Technology Transfer Office at National Jewish Health embodies the spirit of the NJH brand promise, Science Transforming Life®. The Technology Transfer Office accelerates the development of laboratory research towards clinical application by identifying and protecting the institution's intellectual property and facilitating business partnerships for technology licensing and commercialization.

National Jewish has more than 150 technologies in its active portfolio and owns more than 80 issued U.S. patents plus additional corresponding foreign patents.

Attached is a non-exhaustive list of technologies available for licensing from National Jewish.

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TSLP: A Biomarker Predictive of Atopic Dermatitis Development in Infants

NJH ID: #16-06

Background

Atopic dermatitis (AD) is a chronic inflammatory skin disorder that affects nearly 17% of children and can persist into adulthood. Advances in understanding the mechanisms underlying AD require direct sampling of the skin. Because AD is primarily a skin disease involving infants and young children, there are no skin-based studies examining AD in this age group due to the invasiveness of skin biopsies. The abnormal skin barrier in patients with AD allowa epicutaneous absorption of environmental allergens through the skin and promote systemic allergen sensitization, which predisposes to the development of other allergies such as food allergy and asthma.

AD is a complex disease with a genetic predisposition strongly influenced by innate and adaptive immune responses, as well as environmental factors, including allergen exposure, irritants, microbes, diet, stress, and air quality.

To establish a primary prevention strategy for AD, it is important to identify and predict the occurrence of AD. Current treatment approaches are not curative and they include use of strategies to improve skin barrier or downregulate the type 2 allergic immune response. This is why there is considerable interest in developing biomarkers that could predict AD.

Technology

Thymic stromal lymphopoietin (TSLP) is an epithelial cell-derived cytokine expressed in skin (keratinocytes), gut, and lungs. It has a critical role in driving Th2-mediated inflammation by modulating antigen-presenting cells to amplify Type 2 cytokines by T cells and innate lymphoid cells.

In a skin tape stripping study, Dr. Leung and his collaborators demonstrated that increased TSLP expression in the epidermis precedes the development of AD in infants as young as 2 months. Therefore TSLP may serve as an early biomarker for AD.

Potential Applications

TSLP-based diagnostic assay for early identification of infants predisposed to development of AD and predicting patients that will respond to treatment with a TSLP inhibiting agents.

State of Development

Additional skin tape stripping studies will be needed to validate biomarkers which predict infants at risk of developing AD in different racial groups.

Publications

• Epidermal thymic stromal lymphopoietin predicts the development of atopic dermatitis during infancy. J Allergy Clin Immunol. 2016 Apr;137(4):1282-5.e1-4. - PMID: 26879860

Patent Status

US patent pending.

Inventors

Donald Y. M. Leung, MD. PhD; Byung Eui Kim, MD; Kangmo Ahn, MD and Jihyun Kim, MD.

Licensing Status

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Gene panel diagnostic test predictive of ARDS severity

NJH ID: #15-04

Background

There are approximately 150,000 cases of Acute Respiratory Distress Syndrome (ARDS) in the U.S. per year. The severity and survival rate for this disease vary greatly between patients. Therefore, the development of a diagnostic test predictive of clinical outcome may lead to a more personalized and effective treatment of ARDS.

Scientists at National Jewish analyzed genome-wide transcriptional profiles of circulating neutrophils isolated from a prospective cohort study of 120 patients with sepsis-induced ARDS and healthy controls, testing if over- or under-expression of ISG by neutrophils was associated with worse clinical outcomes in patients with ARDS. A novel biomarker panel of three interferon-stimulated genes was identified, predictive of disease severity and prognosis.

Technology

Analysis of the range of neutrophil ISG expression in ARDS patients was correlated with clinical outcomes. Using hierarchical clustering of expression, three distinct subject groups were identified with low, mid and high ISG expression and the three ISG accounting for the greatest variability in expression were identified (*MX1*, *IFIT1*, and *ISG15*). Samples were stratified by standard deviation from the mean and clinical outcomes were compared between patients with high or low ISG expression to those with mid-range expression. After adjusting for age, race, gender and BMI, patients with either high or low ISG expression had significantly worse clinical outcomes than those in the mid-range as determined by number of 28-day ventilator, ICU-free days, 90-day mortality and 90-day home with unassisted breathing.

Potential Applications

Up or down-regulation in neutrophil ISG expression could represent a “window” of vulnerability that places an otherwise healthy subject at increased risk for a period of days or weeks. While neutrophil ISG expression may be of prognostic value at the onset of ARDS, the potential exists for this marker to modify clinical care, either by alerting clinicians to the possibility of an unsuspected viral or autoimmune disease, or as a direct target for immunomodulation through administration of Type 1 interferons. The panel results may provide a method of determining treatment strategy, where the subject is administered a therapeutic effective amount of an ISG suppressing agent is the subject’s ISG expression level is greater than or less than one standard deviation from the mean as compared to the control.

State of Development

The inventors are currently validating this gene panel test using whole blood from ARDS patients, instead of isolated neutrophils.

Publications

Manuscript submitted

Patent Status

US patent pending.

Inventors

Jerry A. Nick, MD and Kenneth C. Malcolm, PhD

Licensing Status

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New biomarkers and targets to Identify and Treat Corticosteroid-Resistant Asthma

NJH ID: #12-12/13-12

Background

Glucocorticoids (GCs) are the most potent anti-inflammatory drugs used for treatment of asthma and other chronic inflammatory or autoimmune diseases. Up to 20% of asthmatics are refractory to GC therapy and are referred to as steroid resistant (SR). SR asthmatics are characterized by increased airway inflammation that cannot be inhibited by GS treatment. Given the variable responses to corticosteroid therapy in asthmatics, alternative therapeutics are needed for personalized treatment of asthma.

Endotoxin or lipopolysaccharide (LPS) exposure, a component of the outer membrane of Gram-negative bacteria, has recently been identified as an important factor that alters cellular response to CS. It has also been implicated in asthma exacerbation.

Intracellular signaling mediated by LPS/TLR4 involves binding of a series of adaptor molecules, and leads to sequential kinase phosphorylation, such as the mitogen and stress activated protein kinase 1 (MSK1) and the transforming growth factor beta associated kinase-1 (TAK-1).

Technology

Dr. Leung's and Dr. Goleva's laboratory identified novel biomarkers associated with asthma resistance to GC. Their lab was able to show in patient samples that elevated levels of phosphorylated MSK1 and/or phosphorylated TAK-1 correlates with resistance to corticosteroid treatment.

They also showed in an in-vitro model that treatment with a TAK-1 inhibitor was able to reverse the steroid resistance.

Potential Applications

Diagnostics: detection levels of phosphorylated TAK-1 and/or phosphorylated MSK-1 in patient blood samples as an indication of corticosteroid resistance.

Treatment: use of TAK-1 and/or MSK-1 inhibitors to reverse steroid resistance in patients with an inflammatory disease.

State of Development

Additional patient samples are being tested to further validate the correlation of these two biomarkers with steroid resistance.

Publications

Goleva et al. Am J Resp Cr Care Med. 2013 Nov 15;188 (10):1193-201.

Patent Status

International Patent Pending

Inventors

Donald Y. M. Leung, MD, PhD and Elena Goleva, PhD

Licensing Status

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Targeting CYP11A1 in the Steroidogenic Pathway For Treating Allergic Diseases

NJH ID: #11-17

Background

CD4 Th2 and CD8 Tc2 cells play a pivotal role in the induction and control of allergic inflammation, including food allergy and asthma. Allergen-specific Th2 CD4+ T cells are essential to the development and maintenance of both type I IgE-mediated and non-IgE-mediated food allergic responses.

Glucocorticoids (GCs) play an important role in the regulation of the immune system. Because of their anti-inflammatory activity GCs are used to treat diseases caused by an overactive immune system, such as allergies, asthma, autoimmune diseases and sepsis. There is accumulating evidence suggesting that GCs can also promote the pathogenesis of allergic diseases by enhancing T-cell pro-allergic differentiation of CD4+T cells to Th2 and Th17, by amplifying immune responses in steroid-insensitive CD8+ T cells and by inhibiting Th1 cytokine production. Endogenous GC synthesis is regulated by the transcriptional control of steroidogenic enzymes of the cytochrome P450 gene family, such as CYP11A1. This particular enzyme converts cholesterol to pregnenolone.

Technology

Dr. Gelfand's laboratory has identified CYP11A1as a key regulator of allergic responses through its effect on steroidogenesis. They demonstrated that CYP11A1 controls the phenotypic conversion of CD4+T cells to Th2 and Th17 and the polarization of CD8+ T cells from an IFN-γ to an IL-13 producing effector cell. Therefore CYP11A1 is a critical regulator of the development of lung allergic responses.

In vitro, both human and mouse CD8+ T cells demonstrated an insensitivity to corticosteroids not seen in CD4+ T cells, supporting the notion that CD8+ T cells are at the root of the failure of asthmatics to respond to corticosteroids and could be responsible for persistent airway hyperresponsiveness (AHR) and airway inflammation.

Gene silencing of CYP11A1 also prevented CD4 Th2 and CD8 Tc2 differentiation.

In a mouse model of peanut allergy, treatment with aminoglutethimide (AMG), an inhibitor of CYP11A1, prevented an allergic response and the accumulation of inflammatory cells in a dose dependent manner. Serum levels of pregnenolone were reduced in parallel.

In an experimental model of asthma, adoptive transfer of AMG-treated CD8+ T cells to sensitized and challenged CD8+ deficient mice prevented AHR and inflammation, in contrast to untreated CD8+ T cells.

These studies identified CYP11A1 as a key regulator of CD8+ Tc2 cell differentiation and plasticity and as a valuable target in the treatment of allergic diseases such as asthma and peanut allergy.

Potential Applications

Treatment or prevention of allergic diseases by administration of CYP11A1 inhibitors such as AMG.

State of Development

Investigators are currently screening libraries to identify molecules that will inhibit CYP11A.

Publications

Wang et al. J Allergy Clin Immunol. 2013 Nov;132(5):1174-1183.e8.
Jia et al. Proc Natl Acad Sci U S A. 2013 May 14;110(20):8152-7.

Patent Status

US and International patents pending.

Inventors

Erwin Gelfand, MD, Meiquin Wang, MD, Ph.D. and Yi Jia.

Licensing Status

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B Cells Desensitization with an Anti-CD79 Antibody: Therapeutic Approach for Autoimmune Diseases

Validated In Vivo

NJH ID: #11-15

Background

B lymphocytes play fundamental roles in the pathogenesis of autoimmune disease as well as transplant rejection. Current technologies for treatment of many lymphomas, leukemias, transplant rejection and some autoimmune disorders include monoclonal antibodies (mAb) that target and deplete B cell populations. Recovery from these treatments requires an extended period of time during which patients are immunosuppressed and therefore susceptible to opportunistic infections. In addition, this modality does not eliminate all B lineage cells and thus may not be appropriate for all pathologic conditions involving B lymphocytes.

Cluster of Differentiation 79 (CD79) is a transmembrane protein found exclusively in B cells that is the transducer component of B-cell receptor (BCR), generating a signal following recognition of antigen by the BCR. As a consequence CD79 is an ideal candidate molecule for B cell-targeted therapy.

Technology

Dr. Cambier and his laboratory discovered that in certain circumstances, subunits of the B cell antigen receptor (BCR) become dissociated rendering the receptor incompetent to transduce activating signals. Based on these observations they produced antibodies against the BCR transducers, CD79a and b, and found that they "desensitize" the BCR and suppress the immune response, autoimmunity, and growth of non-Hodgkin's B lymphoma. These anti-CD79 mAbs show therapeutic potential to induce reversible inhibition of BCR signaling and B cell function. This technology exploits the unique qualities of the BCR to reversibly suppress signaling for therapeutic use in autoimmunity, cancer and transplantation. Receptor desensitization and therapeutic efficacy has been demonstrated in vitro and in vivo.

Potential Applications

- Treatment of autoimmune conditions such as rheumatoid arthritis, lupus, and diabetes
- Treatment of B cell neoplasias
- Prevention of tissue rejection

State of Development

Investigators have shown that administration of an anti-mouse CD79 targeting BCR in a mouse model of lupus, decreased autoantibody production (suppressed B cell responses), decreased skin pathology, and increased survival from 20% to 80%. Furthermore they established that anti-CD79a/b antibodies (intact, or mutants incompetent to bind IgG receptors and activate the complement cascade) block the development of disease and ameliorate ongoing target organ injury in MRL/LPR mouse model of Rheumatoid Arthritis, NOD mice for Type 1 Diabetes and EAE mouse model for MS.

In later experiments they developed a proprietary monoclonal antibody against human CD79 (Curly 14) that has the capacity to desensitize the BCR in vitro.

Further experiments will involve the characterization of the effectiveness of Curly 14 for modulating immune disease, understanding Curly 14 binding affinity, determination of the antibody binding site and the ability to destabilize and/or desensitize B cells in huSCID and human CD79 knockin mouse models.

The creation of a human CD79 expressing mouse model for in-vivo preclinical testing to optimize anti-CD79 therapy is underway. They have successfully produced CD79a and CD79b knockin ES clones, and are currently confirming by doing karyotype analysis.

Publications

Vilen et al. 1997. *J Immunol*. 159(1):231-43. PMID: 9200459

Vilen et al. 1999. *Immunity.* 10:239-248. PMID: 10072076

Li et. al. 2008 *J Immunol*. 1;181(5):2961-72. PMID: 18713966

Hardy et.al. 2014 *J Immunol*. 192(4):1641-50. PMID: 24442438

Brühl et.al. 2014. Eur. J. Immunol. 1521-4141. PMID: 25471597

Patent Status

Issued U.S. Patent #6,503,509 and #7,825,224; Issued patents in France, Germany, UK, Australia and New Zealand; Pending in Canada, and Japan. Human CD79 mAb-related patent pending worldwide.

Inventors

John Cambier, Ph.D. and Barbara J. Vilen, Ph.D, Matt Seefeldt, Ph.D. and Ian Hardy, Ph.D.

Licensing Status

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PTPN13: A Novel Target for the Treatment of Pulmonary Fibrosis

NJH ID: #11-09

Background

Idiopathic pulmonary fibrosis (IPF) is a specific form of chronic, progressive fibrosing interstitial pneumonia, primarily occurring in older adults. It is caused by injury and aberrant repair of the lower lung resulting in accumulation of fibroblasts. These cells produce abundant amounts of collagen and contribute to the formation of scar tissue. In normal wound repair, fibroblasts die and are removed at the completion of the repair process. In IPF, fibroblasts persist and accumulate in the lung, leading to progressive fibrosis, dyspnea, hypoxemia, and death within 5 years of diagnosis.

Technology

Dr. Riches and his group have previously shown that fibroblasts normally die through apoptosis following stimulation of a receptor called Fas. Furthermore they showed that these cells will not die when Fas becomes associated with an inhibitory protein, the PTPN13 molecule. They were able to demonstrate that by blocking the association between Fas and PTPN13, fibroblast cells are once again able to undergo Fas-receptor induced death. These findings suggest that the development of a compound that blocks the Fas/PTPN13 interaction could serve as a therapeutic modality to treat IPF.

Potential Applications

Therapeutic uses for treatment of idiopathic pulmonary fibrosis. Other fibrotic conditions are being explored.

State of Development

Investigators have completed two virtual screens and identified compounds that, based in structural analysis, would be predicted to interfere with the binding of PTPN13 to Fas. In addition, an alpha-screen assay was set up to conduct high throughput screen of the library of small molecule inhibitors.

Publications

- Frankel, Stephen K., Gregory P. Cosgrove, and David W.H. Riches. "TNF-α Sensitizes Normal and Fibrotic Human Lung Fibroblasts to Fas-Induced Apoptosis." American Journal of Respiratory Cell and Molecular Biology 34.3 (2006): 293-304.
- Wynes, Mary W., Benjamin L. Edelman, Amanda G. Kostyk, Michael G. Edwards, Christopher Coldren, Steve D. Groshong, Gregory P. Cosgrove, Elizabeth F. Redente, Alison Bamberg, Kevin K. Brown, Nichole Reisdorph, Rebecca C. Keith, Stephen K. Frankel, and David H.W. Riches. "Increased Cell Surface Fas Expression Is Necessary and Sufficient To Sensitize Lung Fibroblasts to Fas Ligation-Induced Apoptosis: Implications for Fibroblast Accumulation in Idiopathic Pulmonary Fibrosis."J. Immunology 187.1 (2011): 527-37.

Patent Status

US patents pending. Published international patent WO/2012/064763.

Inventors

David Riches, Ph.D., Allison Bamberg, Ph.D.

Licensing Status

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Novel PIM 1 Kinase Inhibitor that Upregulates RUNX3 for the Treatment of Allergic Diseases

NJH ID: #11-06

Background

It is estimated that 50 million people in North America are affected by allergic conditions with an associated cost of more than $10 billion dollars yearly.

The most common form of allergy, allergic rhinitis (nasal allergies), affects about 35 million Americans, 6 million of whom are children. The number of cases of asthma has doubled over the last 20 years affecting 15 million Americans, 5 million of whom are children. Even greater proportionate increases have been seen in atopic dermatitis and food allergy.

Several antagonistic drugs are used to block the action of allergic mediators, or to prevent activation of cells and degranulation processes. These include antihistamines, glucocorticoids, epinephrine (adrenaline), and theophylline. Anti-leukotrienes, such as Montelukast (Singulair) or Zafirlukast (Accolate), are FDA approved for treatment of allergic diseases. Anti-cholinergics, decongestants, mast cell stabilizers, and other compounds thought to impair eosinophil chemotaxis, are also commonly used. Although these drugs help to alleviate the symptoms of allergy to some extent, they play a limited role in chronic treatment of allergic disorders.

Runt-related transcription factors (Runx) are a novel family of transcription factors which are key regulators of lineage-specific gene expression. The data suggest that Runx3 plays a critical role in regulating T-cell development, the differentiation of Th1/Th2 cells and Th1/Th2 cytokine production, and the development of an allergic disease.

Technology

Dr. Gelfand's laboratory at National Jewish Health has shown that the proto-oncogene serine/threonine-protein kinase (PIM-1) increases upon allergen sensitization and is responsible for the downregulation of Runx3. Further, they have shown in mouse models of allergy that the upregulation of Runx3 can be achieved by inhibiting PIM-1 kinase. This strategy substantially reduced allergic responses in mice.

Therefore, upregulating Runx3 by targeting PIM-1 kinase represents a novel approach for treating allergic diseases. Scientists at National Jewish Health and the University of Colorado have also developed novel PIM-1 kinase inhibitors because existing ones suffer from a lack of specificity and problems associated with distribution, metabolism and excretion.

Potential Applications

Treatment of allergic disease by upregulating or sustaining the expression of Runx3.

State of Development

Investigators are currently testing a series of proprietary and novel PIM-1 kinase inhibitors in experimental models of asthma, allergic rhinitis and peanut-induced food allergy in mice.

Publications

- Frankel, Stephen K., Gregory P. Cosgrove, and David W.H. Riches. "TNF-α Sensitizes Normal and Fibrotic Human Lung Fibroblasts to Fas-Induced Apoptosis." American Journal of Respiratory Cell and Molecular Biology 34.3 (2006): 293-304.
- Wynes, Mary W., Benjamin L. Edelman, Amanda G. Kostyk, Michael G. Edwards, Christopher Coldren, Steve D. Groshong, Gregory P. Cosgrove, Elizabeth F. Redente, Alison Bamberg, Kevin K. Brown, Nichole Reisdorph, Rebecca C. Keith, Stephen K. Frankel, and David H.W. Riches. "Increased Cell Surface Fas Expression Is Necessary and Sufficient To Sensitize Lung Fibroblasts to Fas Ligation-Induced Apoptosis: Implications for Fibroblast Accumulation in Idiopathic Pulmonary Fibrosis."J. Immunology 187.1 (2011): 527-37.
- Gelfand, Erwin W., and Meiqin Wang. "Targeting Pim1 kinase in the treatment of peanut allergy." National Center for Biotechnology Information. U.S. National Library of Medicine, 02 Feb. 2014.

Patent Status

US and International patents pending. Published US-2012-0114663-A1.

Inventors

Erwin Gelfand, MD and Meiquin Wang, MD, Ph.D.

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Novel Adjuvant for Increasing Effectiveness of Vaccines

NJH ID: #10-13

Background

Most current vaccines, including those against influenza, act via the generation of specific antibodies that can either neutralize or otherwise inactivate the pathogen. These vaccines induce the production of antibodies against viral surface proteins to prevent viral cellular entry. However, as far as influenza is concerned, these viral surface proteins tend to mutate over time and as a result a new vaccine against influenza must be developed every year. To avoid this problem, the ideal vaccine would be pan-specific across strains of influenza virus.

Targeting CD8 T cell mediated immunity could be the right strategy to reach this goal. The portions of influenza virus that are recognized by cytotoxic CD8 T cells are much less variable than those recognized by antibodies. Thus a vaccine designed to activate CD8 T cells has the potential to protect against yearly and newly emerging pandemic viral subtypes.

Technology

Dr. Marrack's laboratory at National Jewish Health has discovered how to prime a second arm of the immune system to boost the effectiveness of influenza vaccines. They demonstrated that the combination of two adjuvants (alum and monophosphoryl lipid A, MPL), already approved f3or patient use, with a viral nuclear protein can maintain long-lived memory CD8 T cells and protect mice from influenza viral challenge.

Potential Applications

A combination of two adjuvants, such as alum and MPL, with an internal viral protein can be used to induce CD8, (killer) T cells to join antibodies in response to viral infection. CD8 T cell epitopes are much less variable and thus a vaccine designed to activate protective CD8 T cells has the potential to protect against yearly and newly emerging pandemic viral subtypes. This new approach could be applicable to infectious disease such as the flu and malaria.

State of Development

Investigators have tested the combination of adjuvants (alum and MPL) in a mice model of Influenza A infection. Mice primed with nucleoprotein of influenza A (NP) and both adjuvant lost less weight and quickly regained their original weight in contrast to mice primed with NP/protein and either adjuvant.

Publications

• Macleod, M. K. L., A. S. Mckee, A. David, J. Wang, R. Mason, J. W. Kappler, and P. Marrack. "Vaccine Adjuvants Aluminum and Monophosphoryl Lipid A Provide Distinct Signals to Generate Protective Cytotoxic Memory CD8 T Cells."PNAS 108.19 (2011): 7914-919.

Patent Status

US patent pending. Published international patent WO 2011/057267.

Inventors

John W. Kappler Ph.D., Philippa Marrack Ph.D., Meghan MacLeod, Ph.D., Amy McKee.

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A p60 Polypeptide Variant Stimulates NK Cells and Reduces Tumor Size In Vivo

NJH ID: #10-08

Background

Natural killer cells (or NK cells) are cytotoxic lymphocytes that, when appropriately activated, play a major role in the rejection of tumors and cells infected by viruses. NK cells kill infected or cancerous target cells by releasing small cytoplasmic granules of proteins called perforin and granzyme that cause the target cell to die by apoptosis (programmed cell death). They also secrete cytokines that can regulate innate and adaptive immune responses. Thus, strategies to therapeutically activate NK cells have potential use in treatment of infections and tumors and improving adaptive immune responses to these agents and vaccines. Since activated NK cells also contribute to successful pregnancy, such strategies might also be used to promote successful full-term pregnancy.

There are currently few therapeutically viable strategies to activate NK cells in patients. Use of non-specific immune stimulants such as Toll-like receptor (TLR) agonists are minimally effective and elicit toxicity. Antibodies to certain NK cell surface markers are in some cases effective, but target specific NK cell subsets and may not work in all patients due to allelic differences in NK cell surface proteins recognized by the antibodies. Antibodies may also cause depletion of NK cells or only activate specific functions of NK cells. We have developed an approach for activating a large proportion of mouse and human NK cells under conditions conducive to effective therapy.

Technology

All species of the genus Listeria secrete a major extracellular protein called p60. The laboratory of Dr. Lenz at National Jewish Health has shown that the wildtype p60 protein promotes NK cell activation and created a mutant form of p60 that retains this ability to activate NK cell but lacks enzymatic endopeptidase activity that could result in unwanted side effects when the protein is administered to patients. They found that both forms of p60 contribute to the activation of naïve mouse and human NK cells due to the ability of p60 to appropriately stimulate another immune cell type, dendritic cells (DC).

Potential Applications

Treatment of diseases that will benefit from NK cells activation:

- *Cancer*. Evidence points to a positive association between NK cell activation and positive outcomes in solid, metastatic and hematologic cancers.
- *Infectious diseases*. NK cells are implicated in resistance to numerous viral infections prevalent in the US and other countries; including upper respiratory infections, HSV, EBV, VZV, HPV, CMV.
- *Vaccines*. P60 appears to act directly on naïve DCs to stimulate their maturation in a manner that permits activation of NK cells. Both activated DCs and IFN□ that is produced by NK cells can boost cellular (Th1-type) immune responses. P60 may be useful to improve immune responses elicited by vaccines and thus be useful for vaccinating large numbers of people world wide.
- *Pregnancy*. NK cells are found in the placenta and their activation has been associated with positive pregnancy outcome. There may be utility in stimulating NK cell function with p60 to prevent pre-eclampsia and improve pregnancy success in individuals suffering recurrent miscarriages.

State of Development

Investigators at NJH have identified a region of the p60 protein that is necessary and sufficient to elicit NK cell activation. Small polypeptides that contain this region retain functionality and when administered to mice reduce tumor size in a cancer model. Modified versions of these polypeptides may show increase stability (and thus activity).

Publications

- Schmidt et al. PLoS Pathog. 2011 Nov;7(11):e1002368.
- Schmidt et al. PLoS One. 2012;7(9):e45186.

Patent Status

US patent pending. Published international patent WO 2011/060093.

Inventors

Laurel L. Lenz, Ph.D., Rebecca Schmidt, Ph.D.

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Anti CD19/CD11c Bi-Specific Antibodies Target a Subset of B Cells to Treat Autoimmune Diseases

NJH ID: #09-03

Background

It is estimated that 23.5 million Americans suffer from autoimmune disease (AD) and that the prevalence is rising. Researchers have identified 80-100 different ADs and suspect at least 40 additional diseases of having an autoimmune basis. These diseases are chronic and can be life-threatening with an annual direct health care costs in the range of $100 billion. AD is one of the top 10 leading causes of death in female children and women in all age groups up to 64 years. Current therapies for autoimmune diseases such as immunosuppressant treatments, anti-CD20 and anti-TNF monoclonal antibodies (mAb) have very profound effects on the whole immune system leading to substantial long-term side effects. These therapies deplete patients of large populations of immune cells that are important for maintaining the integrity of the host response to pathogens.

Technology

Researchers at National Jewish Health have identified a new population of autoimmune associated B cells (ABCs) that appears in the blood and lymphoid organs as the mice develop an autoimmune disease.
They further demonstrated that ABCs secrete autoantibodies and depletion of these cells in mice with ongoing autoimmunity leads to reduction of autoreactive antibodies, suggesting that ABCs play a direct role in the development of autoimmunity. This population of cells also increase in female mice as they get older, possibly explaining why females are more likely to develop autoimmunity compared to males. Furthermore, they were able to identify B cells in the blood of autoimmnune patients with a phenotype almost identical to those of ABCs in mice.

Potential Applications

Diagnostic: early detection of ABCs in blood will make possible for physicians to identify patients developing autoimmunity before the onset of symptoms, allowing for earlier and more successful therapeutic interventions.
Therapeutic: targeted depletion of ABC cells with a bispecific (CD19/CD11c) mAb could lead to the development of a treatment for autoimmune diseases.

State of Development

Fusion hybridomas have been created and the best bispecific antibodies will be isolated and tested for their binding capacity and then for ability to deplete ABCs. These antibodies recognize two different proteins (CD19 and CD11c) on the surface of ABCs and will be tested in a mouse model of autoimmunity. This therapeutic approach will lead to the specific elimination of ABCs with no effect over other B cells, modeling a potential treatment in which the individuals being treated are much less immune compromised than with current treatments where all B cells are depleted.

Publications

- Rubtsov, A. V., K. Rubtsova, A. Fischer, R. T. Meehan, J. Z. Gillis, J. W. Kappler, and P. Marrack. "Toll-like Receptor 7 (TLR7)-driven Accumulation of a Novel CD11c B-cell Population Is Important for the Development of Autoimmunity." Blood 118.5 (2011): 1305-315.
- Rubtsov, Anatoly V., Kira Rubtsova, John W. Kappler, and Philippa Marrack. "TLR7 Drives Accumulation of ABCs and Autoantibody Production in Autoimmune-prone Mice."Immunologic Research 55.1-3 (2013): 210-16.

Patent Status

US patent pending. Published international patent WO 2010/054288.

Inventors

John W. Kappler Ph.D., Philippa Marrack Ph.D., Anatoly Rubtsov, Ph.D. and Julia Rhiannon, M.D.

Licensing Status

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Blood Biomarkers Determine Therapeutic Response in Cystic Fibrosis Patients

NJH ID: #08-22

Background

Cystic fibrosis (CF) is a genetic disorder that affects one out of every three thousand newborns. It is the most common lethal inherited disease in the western world. The life expectancy for this disease has increased to nearly 40 years and respiratory failure is the main cause of death in this patient population.

The major complications in CF are airway obstruction with mucus, chronic endobronchial infection with pathogens such as Pseudomonas aeruginosa, and severe airway inflammation. Acute pulmonary exacerbations are also common in CF and contribute to loss of lung function.

There is a critical need for new effective anti-microbial and anti-inflammatory therapies to mitigate the progression of this disease. However, assessment of treatment outcomes is currently limited to standard practices based on Forced Expiratory Volume (FEV1) and C-Reactive Protein (CRP) measurements. This approach lacks sensitivity and therefore is not suitable to reliably determine the efficacy of drug treatments in CF patients or other diseases associated with airway inflammation.

Technology

Physician scientists at National Jewish have identified a novel panel of leukocyte gene biomarkers associated with pulmonary inflammation. A clinical study performed in cystic fibrosis patients at National Jewish showed that circulating leukocytes transcripts of this gene panel is particularly useful in quantifying therapeutic response and predicting disease resolution. This blood-based diagnostic test is highly reproducible across patient groups and can differentiate between acutely ill and subsequent treated patients. This test is able to quantify reduction in pulmonary infection and inflammation following treatment with greater accuracy than standard measurements such as FEV(1) and CRP.

Potential Applications

Diagnostic test for measuring drug response in any lung related disease were inflammation, exacerbation or pulmonary infection is present.

State of Development

The test has been validated with CF patient samples.

Publications

- Saavedra, M. T. et al. "Circulating RNA Transcripts Identify Therapeutic Response in Cystic Fibrosis Lung Disease." American Journal of Respiratory and Critical Care Medicine 178.9 (2008): 929-38. PMID: 18723435.
- Nick, J. A. et al. "Blood MRNA Biomarkers for Detection of Treatment Response in Acute Pulmonary Exacerbations of Cystic Fibrosis." Thorax 68.10 (2013): 929-37. PMID: 23783371.

Patent Status

Issued U.S. Patents #8,101,361 and #8,465,923. Other US patents pending

Inventors

Milene Saavedra, MD and Jerry Nick, MD

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Novel Lipid Inhibitors of TLR Effective at Reducing RSV and Influenza A Infection In Vivo

NJH ID: #07-07

Background

Respiratory Syncytial Virus (RSV) is the most common cause of hospitalization for respiratory illness in young children and 90% of children under the age of 2 will be infected by this virus. RSV infection and associated inflammation have also been shown to be a substantial contributing factor in the exacerbation of chronic lung diseases in adults and the elderly. Influenza A virus (IAV) is a worldwide public health problem causing 500,000 deaths each year with the highest death rates among newborns, the elderly and adults with chronic lung diseases.

Technology

Dr. Voelker's lab at National Jewish Health has demonstrated the anti-inflammatory and anti-viral properties of unsaturated phosphatidylglycerols (PGs). PGs markedly attenuate pro-inflammatory cytokine production (IL-6, IL8) induced by RSV, and prevent viral replication in human bronchial epithelium. In addition these researchers have shown that PGs prevent the intercellular spreading of the RSV virus, after infection is established. Studies with mice reveal that treatment with PGs at the time of viral challenge dramatically reduces RSV infection.
Further studies by these scientists have also shown that PG attenuates influenza virus induced cytokine production in human bronchial epithelial cells; and intranasal administration of PG suppresses influenza A virus infection in mice.
The Voelker laboratory has also created 4 novel compounds with similar activity to that of PGs. These novel compounds block RSV and influenza A attachment to epithelial cells in vitro without apparent toxicity.

Potential Applications

Respiratory Syncytial Virus (RSV), influenza A virus, rhinovirus, sepsis-induced ARDS, asthma, reducing the effects of inflammation during mechanical ventilation, chronic bronchitis, COPD, cystic fibrosis, idiopathic pulmonary fibrosis

State of Development

The lab is now working on continuous delivery systems for liposomes using aerosol techniques, and will use this method to improve the window of efficacy of the PGs. Four novel compounds are undergoing a toxicology study with a mouse model of RSV infection.

Publications

- Kuronuma et al. J Biol Chem. 2009 Sep 18;284(38):25488-500. Epub 2009 Jul 7. PMID: 19584052.
- Numata et al. Proc Natl Acad Sci U S A. 2010 Jan 5;107(1):320-5. Epub 2009 Dec 22. PMID: 20080799.
- Kandasamy et al. J Biol Chem 286:7841 2011 PMID: 21205826.
- Numata et al. Am J Respir Cell Mol Biol. 2011 PMID: 22052877.
- Numata et al. J Lipid Res. 2013 Aug;54(8):2133-43. PMID: 23749985.
- Numata et al. Int J Nanomedicine. 2013;8:1417-27. Epub 2013 Apr 15. PMID: 23717040.
- Numata et al. Expert Rev Respir Med 2012 Jun;6(3):243-6. PMID: 22788936.

Patent Status

U.S. Patent #8,367,643.
Published U.S. patent application #20080242640. International patents pending.

Inventors

Dennis R. Voelker, Ph.D.

Licensing Status

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MAGP-2: An Extracellular Factor Shown To Have Pro-Angiogenic Properties In Vivo

NJH ID: #06-05

Background
Excessive angiogenesis has emerged as an essential feature of tumor development and appears to be regulated in part by extracellular matrix proteins. Scientists at National Jewish Health have identified an extracellular matrix protein (designated MAGP-2) that acts as a pro-angiogenic agent in vivo.

Potential Applications
A target for inhibiting angiogenesis in cancer and other angiogenesis-dependent diseases
Stimulating neovascularization by administration of MAGP-2 to ischemic tissues in coronary artery disease, stroke, and delayed wound healing
A diagnostic biomarker, especially for cancer

Advantages of Invention
Because of its extracellular nature, MAGP-2 can be easily detectable and targetable by antibody-based technologies for example.

State of Development
Our scientists have shown the following:
In vitro:
MAGP-2 is over expressed in human uterine tumor samples
Endothelial cell expression of MAGP-2 increases during angiogenesis in vitro
MAGP-2 stimulates angiogenic sprouting in 3-dimensional collagen cultures
MAGP-2 increases endothelial cell proliferation and invasion in vitro
In vivo:
Significant enhancement of neovascularization when MAGP-2 was implanted into mice through matrigel plugs
MAGP-2 increases tumor size and angiogenesis in mice

Publications

- Albig, Allan R., Thessa G. Roy, Darryl J. Becenti, and William P. Schiemann. "Transcriptome Analysis of Endothelial Cell Gene Expression Induced by Growth on Matrigel Matrices: Identification and Characterization of MAGP-2 and Lumican as Novel Regulators of Angiogenesis." Angiogenesis 10.3 (2007): 197-216. PMID: 17632767.
- Albig, Allan R., Darryl J. Becenti, Thessa G. Roy, and William P. Schiemann. "Microfibril-associate Glycoprotein-2 (MAGP-2) Promotes Angiogenic Cell Sprouting by Blocking Notch Signaling in Endothelial Cells." Microvascular Research 76.1 (2008): 7-14. PMID: 18417156.

Patent Status
U.S. Patents #8,158,107 and #8,629,107, additional U.S. patents pending.

Inventors
William P. Schiemann, Ph.D. and Allan Albig, Ph.D.

Licensing Status
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Method to Prevent Biofilm Formation

NJH ID: #04-08

Background

Researchers at National Jewish Health have determined that actin originating from necrotized human neutrophils serve as a biological matrix in the formation of microbial biofilms in the airways of cystic fibrosis (CF) patients. Since biofilm formation allows for the survival of microbial organisms in the airways of CF patients and is also associated with increased morbidity and mortality, targeting actin and/or neutrophils could be the basis for the development of a potential therapy for CF.

Technology

Targeted therapy for preventing or reducing biofilm formation in cystic fibrosis, infectious kidney stones, cystitis, dental caries, chronic otitis media, bacterial endocarditis, osteomyelitis, wounds, and acne
Prevention of microbial biofilm development on contact lenses, orthopedic implants, stents, catheters and other medical devices
An assay to test compounds for their ability to prevent/reduce biofilm formation by assessing the ability of microbial organizations to bind actin

Advantages of Invention

This therapy, focused on biofilm prevention or degradation, is particularly applicable for early stage CF in young patients when antimicrobial agents are only partially effective at best.

State of Development

Our scientists have shown the following in vitro:

- Biofilm development of P. aeruginosa is enhanced with:
  - the addition of human viable neutrophils and correlates with an increase in the number of necrotic neutrophils.
  - the addition of neutrophils lysates and particularly with monomeric actin (G-actin).
- Biofilm development of P. aeruginosa is reduced with:
  - the addition of neutrophils lysates depleted of actin microfilaments (F-actin).
  - the addition of compunds that promotes the depolymerization of F-actin, such as gelsolin or charged poly(amino acids).

Further R&D Required

Using the state grant to identify the most effective charged poly(amino acids) at disrupting biofilms and testing such compounds on infected contact lenses, and in animal models of eye and skin infections.

Publications

- Walker, T. S., K. L. Tomlin, G. S. Worthen, K. R. Poch, J. G. Lieber, M. T. Saavedra, M. B. Fessler, K. C. Malcolm, M. L. Vasil, and J. A. Nick. "Enhanced Pseudomonas Aeruginosa Biofilm Development Mediated by Human Neutrophils." Infection and Immunity 73.6 (2005): 3693-701. Print. PMID: 15908399.
- Parks, Q. M., R. L. Young, K. R. Poch, K. C. Malcolm, M. L. Vasil, and J. A. Nick. "Neutrophil Enhancement of Pseudomonas Aeruginosa Biofilm Development: Human F-actin and DNA as Targets for Therapy." Journal of Medical Microbiology 58.4 (2009): 492-502. PMCID: PMC2677169.
- Robertson, D. M., Q. M. Parks, R. L. Young, J. Kret, K. R. Poch, K. C. Malcolm, D. P. Nichols, M. Nichols, M. • Zhu, H. D. Cavanagh, and J. A. Nick. "Disruption of Contact Lens-Associated Pseudomonas Aeruginosa Biofilms Formed in the Presence of Neutrophils." Investigative Ophthalmology & Visual Science 52.5 (2011): 2844-850. PMID: 21245396.

Patent Status

U.S. Patents #8,753,662 and #8,901,167.
International Patent Application #WO2006/017816. Additional patents pending.

Inventors

Jerry A. Nick, M.D.; Travis S. Walker; G. Scott Worthen, M.D.; and Quinn Parks, Ph.D.

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Modulating the Transport of Thiol-Containing Molecules for the Treatment of Lung Diseases and Cancer

NJH ID: #02-16

Summary

National Jewish scientists have identified families of compounds that can increase the transport of thiol-containing molecules, like glutathione, from the cell. Cystic fibrosis and a number of inflammatory lung diseases share a diminished level of glutathione in the epithelial lining fluid and excessive lung inflammatory response. The compounds identified have shown to increase endogenous glutathione in the epithelial lining fluid and therefore could decrease oxidative damage in these diseases. Increasing glutathione efflux is also beneficial in sensitizing cancer cells to anti-cancer agents that cause oxidative damage. These discoveries form the basis of a novel drug discovery platform that modulates oxidative stress in human disease.
Treatment with these compounds in mice increased the levels of glutathione in the extracellular compartment and the lung epithelial lining fluid (ELF). Significant multidrug resistance-associated proteins-specific efflux of glutathione has also been demonstrated in cancer cell lines with a concomitant potentiation of cisplatin cytotoxicity.

Potential Applications

Lung diseases, such as cystic fibrosis, chronic beryllium disease, sarcoidosis, idiopathic pulmonary fibrosis, acute respiratory distress syndrome, chronic obstructive lung diseases, idiopathic interstitial pneumonia, and diffuse fibrosing alveolitis.
Adjuvant therapeutic in radiation or chemotherapy treatment for cancer.

Advantages of Invention

Many of the compounds are well known and characterized, including one that is currently approved and marketed for unrelated indications.
Compartment and tissue specific secretion of thiol-containing molecules.
An improvement over treatment with exogenous glutathione, which has a short half-life, poor bioavailability, and a lack of stability.

State of Development

In mice, treatment with these compounds increased the levels of glutathione in the extracellular compartment and the lung epithelial lining fluid (ELF). Significant MRP-specific efflux of glutathione has also been demonstrated in cancer cell lines with a concomitant potentiation of cisplatin cytotoxicity.

Further R&D Required

Additional in vivo studies with other animal models.

Publications

- Day BJ et al. Infect Immun. 2004 Apr; 72(4):2045-51. PMID: 15039325
- Day BJ et al. Am J Physiol Lung Cell Mol Physiol. 2001 Jul; 281(1):L31-8. PMID: 11404242
- Kachadourian et al. Int J Oncol. 2007 Jul; 31(1):161-8. PMID: 17549417
- Kachadourian et al. Biochem Pharmacol. 2007 Dec 15; 74(12):1677-85. Epub 2007 May 21. PMID: 17585883
- Kachadourian et al. Free Rad Bio & Med 2006; 41:65-76. PMID: 16781454

Patent Status

Issued U.S. Patent #7,498,047
Published U.S. Patent Application #20060135585; International Publication #WO2004/042020; other U.S. and international patents pending.

Inventors

Brian Day, PhD, Leonard Velsor, PhD and Remy Kachadourian, PhD

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Liposomal Clodronate as a Therapy for Autoimmune Hemolytic Anemia

NJH ID: #02-07

NOTE: THIS TECHNOLOGY IS EXPERIMENTAL AND THEREFORE IT IS NOT AVAILABLE TO HUMANS. IT HAS ONLY BEEN TESTED IN MICE AND DOGS DIAGNOSED WITH AIHA

Summary

Our scientists have shown that treatment with liposomal clodronate substantially decrease red blood cell destruction in animals that were giving anti red blood cell antibodies. This effect was detected within hours and lasted at least a week. The efficacy has been demonstrated in vivo in a mouse model. This therapeutic approach also showed high efficacy and no toxicity in dogs affected with autoimmune hemolytic anemia.
The therapy could be used for humans and companion animals.

Potential Applications

Therapy for autoimmune hemolytic anemia
The therapy is applicable to both humans and companion animals

Advantages of Invention

The method is less invasive than surgery (splenectomy)
Decrease use of steroids
Decrease side effects

State of Development

The efficacy of this therapy has been demonstrated by some strong in vivo data obtained in mice and dogs with AIHA. Using a mouse model in which animals were given anti red blood cell antibodies, treatment with liposomal clodronate substantially decreased red blood cell destruction.
In addition, this effect was detected within hours and lasted at least a week.

Further R&D Required

Additional in vivo studies with other animal models.

Licensing Potential

Available for licensing.

Publications

• Jordan, M. B., John Kappler, and Pippa Marrack. "Liposomal Clodronate as a Novel Agent for Treating Autoimmune Hemolytic Anemia in a Mouse Model." Blood 101.2 (2002): 594-601. Print. PMID: 12393630.
• Mathes, Mark, Michael Jordan, and Steven Dow. "Evaluation of Liposomal Clodronate in Experimental Spontaneous Autoimmune Hemolytic Anemia in Dogs." Experimental Hematology 34.10 (2006): 1393-402. Print. PMID: 16982332

Patent Status

U.S. Patent #7,090,865.

Inventors

Mike Jordan, MD, Philippa Marrack, PhD and John Kappler, PhD.

Licensing Status

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Tall-1 and it's Receptor BCMA: Therapeutic Targets for Autoimmune Diseases

NJH ID: #02-01

Summary

Researchers at National Jewish Health have discovered that TALL-1, a member of the tumor necrosis factor (TNF), plays an important role in the modulation of immune responses by costimulating B lymphocyte proliferation. TALL-1 has been crystallized and its 3D structure resolved. In addition, the investigators have isolated a receptor at the surface of B lymphocytes, B cell maturation protein (BCMA), that specifically binds to TALL-1. Various TALL- induced genes have also been identified. Therefore, BCMA, the 3D structure of TALL-1and TALL-1-induced genes can constitute several target routes for the development of treatments against autoimmune diseases.

Potential Applications

Therapy for inflammatory and immune-related diseases.

Advantages of Invention

Novel extracellular targets

State of Development

National Jewish Health scientists have demonstrated the following:

- TALL-1 is expressed specifically in monocytes and macrophages
- TALL-1 is down regulated by mytogens
- BCMA specifically binds to TALL-1 and activates NF kappaB through a TRAF5/TRAF-6 pathway
- The 3D structure of the TALL-1 monomer by crystallography
- 60 TALL-1 monomers can form a virus like structure in physiological conditions
- The TALL-1 region critical for the formation of this virus-like structure has been identified
- Deletion of such region disrupts the virus like assembly but does not affect the binding to BCMA and the NF-kappaB activation
- Several genes have been identified and shown to be induced by TALL-1 and NF-kappaB dependent

Further R&D Required

The investigators have created a Fc-BCMA mutant that has increased avidity and specificity to B lymphocytes. This is currently being tested in mice models of autoimmune diseases.

Licensing Potential

Available for licensing.

Publications

- Shu et al. (1999) J. Leukoc. Biol. 65(5): 680-683
- Shu and Johnson (2000) Proc. Natl. Acad. Sci.97(16): 9156-9161
- Liu et al. (2002) Cell. 108: 383-394
- Xu et al. (2002) J. Leukoc. Biol. 72(2): 410-416
- Liu et al. (2003) Nature. 423: 49-56

Patent Status

U.S. Patents #6,475,987, #7,825,089 and #7,994,115. Published U.S. Patent Application #20070015695 and US Application #WO2003/35846, other U.S. and international patents pending covering TALL-1 and its 3D structure, BCMA and homologues, and methods of use.

Inventors

Hong-Bing Shu, Ph.D., Gongyi Zhang, Ph.D.

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