Arizona Asthma Research Platform Strategic Plan

March 2007

Table of Contents

I. Strategic Vision and Focus for Asthma Platform

STRATEGIC VISION

Arizona will help transform the field of asthma research by focusing on advancing a presymptomatic understanding of the disease process and preventive interventions that reach far beyond existing clinical and therapeutic approaches that focus primarily on addressing asthma's cause and symptoms. By establishing a statewide Asthma Research Consortium, Arizona can tackle this ambitious goal that builds on existing research and clinical strengths and knowledge of environmental exposures in asthma found across the state. Key to the success of the Arizona Asthma Consortium will be leveraging Arizona's broader bioscience technology efforts in genomics and molecular diagnostics/therapeutics along with the development of a shared research capacity in applied human immunology that serves as the translational link between genomics and diagnostics/therapeutics.

THE CHALLENGE OF ASTHMA RESEARCH

Asthma is a complex and chronic respiratory disorder affecting both children and adults that results in troubled breathing due to inflammation and constriction of the bronchial airways. The disease is a significant and growing health burden. Data from the National Health Interview Survey indicate that approximately 20 million Americans suffer from asthma, and office visits for asthma increased from 5.9 million in 1980 to 10.8 million in 1999. The National Heart, Lung and Blood Institute reports that more than 5,000 people die of asthma annually. Dorland Healthcare Information reports that the cost of treatments for asthma rose from $11.8 billion in 2000 to $17.1 billion in 2003, an average annual increase of over 11%. In

Arizona, AZHealthQuery (AZHQ) reports that 5% of adults and 8% of children in Maricopa County have asthma.

Despite the significance of asthma as a chronic disease, the basic disease processes of asthma are still largely unknown. Asthma today is largely defined by the symptoms involving "airway obstruction" with the main symptoms including coughing, wheezing, chest tightness, shortness of breath, and mucus production, but a precise definition of asthma and knowledge of the processes that lead to these symptoms are lacking. While it is agreed that asthma is a result of immune system dysfunction, a more complete understanding of disease processes and how existing treatments "turn off" the immune system in the lungs is critical for building immunological knowledge. This knowledge could lead to the discovery of new "biosignatures," biological indicators specific to an individual's health status or disease state. It could also lead to identification of treatments targeted to the affected organ (e.g., lung) rather than systemic treatments.

How Asthma is Treated Today

In addition to patient education and attempts to eliminate triggers, current asthma treatments generally focus on relief of symptoms and long-term regimens for preventing future attacks:

Relief
- Fast-acting bronchodilators

Prevention
- Anti-inflammatory medications such as inhaled steroids
- Leukotriene receptor antagonist medications

An understanding of the underlying immunological basis of asthma could yield strategies for preventing asthma before symptoms ever occur.

According to the NIH, treatment goals should include the prevention of symptoms, maintenance and/or restoration of normal lung function, and minimal side effects. Current treatment strategies focus primarily on relief of symptoms and prevention of future asthma attacks. Novel treatment strategies that aim to prevent symptoms from occurring in the first place will require a clear understanding of the underlying immunological, genetic, environmental or viral components of the disease. Asthma involves a complex disease process with considerable interaction between multiple factors including genetics and the environment. However, simply knowing a person's genetic predisposition to asthma or to reactions to environmental allergens is not sufficient to understand whether the disease will be realized, nor the type of disease that will be encountered.

How Asthma is Understood Today

The National Heart, Lung and Blood Institute classifies asthma today into four categories based on the severity of symptoms … with little knowledge of the disease processes underlying the severity of how the disease progresses:

- Severe Persistent – Continual symptoms, limited physical activity and frequent exacerbations
- Moderate Persistent – Daily symptoms, daily use of inhalants, exacerbations affect activity and occur more than twice a week
- Mild Persistent – Symptoms more than twice a week, but less than one time a day and exacerbations may affect activity
- Mild Intermittent – Symptoms less than twice a week, exacerbations brief and intensity varied

What are needed are both a basic understanding of the immunology and progression of the disease, and a better diagnosing and treating an individual patient's specific condition. The challenge of asthma research is thus to decipher the basic underlying

mechanisms that characterize asthma onset and progression, identify biosignatures indicative of predisposition, and develop methods for intervening with patients' immune systems prior to or at the first sign of asthma symptoms.

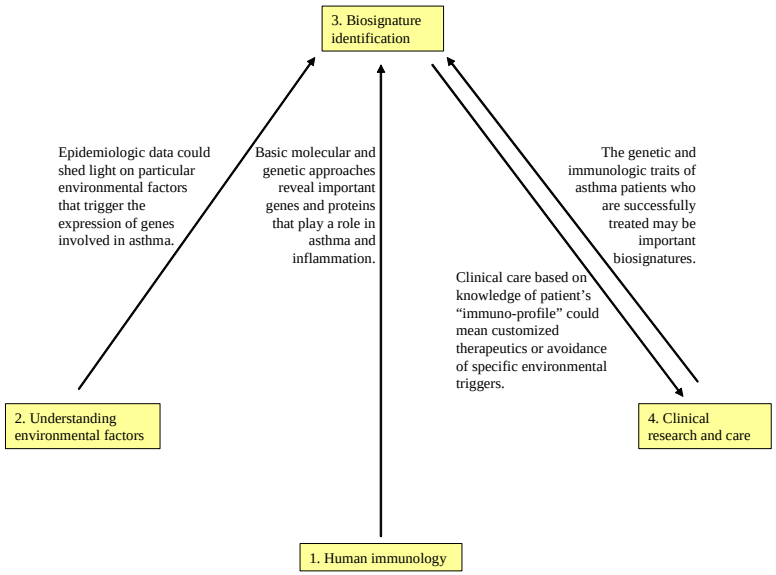
IDENTIFIED APPROACH FOR ADVANCING ARIZONA'S ASTHMA RESEARCH PLATFORM

The Asthma Platform should take an aggressive, transformative "risk-taking" approach leveraging basic research, clinical research and clinical care found in Arizona.

The proposed approach is fourfold:

1) Advance identification of human immunological targets and processes in asthma
2) Understand the contributions of specific environmental factors
3) Improve the definition, diagnosis and approach to treatment of asthma through "biosignature" research
4) Administer clinical care based on knowledge of patient immunosignatures

Together, this four-prong approach would allow Arizona to take a leadership role in using advanced technologies in biosignature diagnostics, vaccine development and systems biology to advance a prognostic definition of asthma, learn more about the underlying disease mechanisms, link the disease process to genetic traits and to measurements in blood and breath, understand the role of the environment in the disease process, and pursue personalized drug treatments.



FOUR MAIN TENETS OF ARIZONA'S APPROACH:

- **Developing a shared statewide core in human immunology in basic and clinical research**. In essence, asthma is the result of an abnormal immune response in the bronchial airways. The airways of asthmatics are "hypersensitive" to certain triggers (smoke, dust, pollen, etc.), which cause the airways to spasm and inflammation to occur and further narrow the airways and produce mucus leading to coughing and other breathing difficulties.

  Critical elements to examine in advancing the understanding of asthma from an immunological perspective include:

  - The pathogenesis of asthma or what factors determine the disease; and
  - How the immune system modulates over time as the disease symptoms are turned on and off and as the disease progresses.

  The main focus of immunology-based asthma research should focus on identifying markers that could prevent the occurrence of asthma and its symptoms ("cut asthma off at the pass"). Asthma is not a disease; rather it is a manifestation of symptoms that can be initiated by multiple factors. Sub areas of immunology that lead to the "smart" approach of prevention were:

  - Inflammatory inhibitors
  - Inflammatory markers
  - Immunological genetics

  The approach should encompass not only basic immunology, but immunology as a conduit for advancing clinical applications through use of new and emerging technologies. In other words, immunology will serve as a link between genomics and clinical research such that genomics research will focus on the identification of immunological targets for intervention, and clinical research will focus on the identification of patient groups who respond to treatment and who may therefore have unique immunosignatures that can be exploited for advances in therapy.

  This capacity in human immunology is currently a missing element within the Arizona biosciences research community. Developing it as a core research center will allow for other immune and inflammatory related disease areas to benefit from this new capacity of immunology, such as:

  - Arthritis
  - Type I diabetes
  - Autoimmune thyroiditis
  - SLE - Systemic lupus erythematosus
  - Other autoimmune diseases
  - Responses to vaccines

- **Understanding the contribution of environmental factors and conditions to asthma susceptibility, progression and treatment.** While certain genetic traits predispose individuals to the development of asthma, exposure to environmental

agents also contributes to the development, progression and severity of the disease. Symptoms can be triggered by a variety of environmental agents including air pollutants, dust and allergens. However, to improve the diagnosis and treatment of asthma, a better understanding of each of the following is needed:

- How individuals with specific genetic traits respond to exposure;
- How environmental agents act at the molecular level on the expression of genes implicated in asthma development; and
- Whether exposure not only precipitates symptoms in individuals who are already predisposed, but can also induce asthma in individuals who lack genetic predisposition and would not otherwise develop the disease.

How individuals develop tolerance to environmental agents is another question that needs to be addressed. During tolerance, the immune systems of non-asthmatic individuals recognize that innocuous particles in the environment are not dangerous, and refrain from attacking. However, tolerance is not established in asthmatic individuals, whose immune systems attack these particles, triggering the inflammatory process that leads to the familiar symptoms of asthma. Insight on how tolerance is developed could lead to novel treatment strategies.

Existing resources that will play key roles in this field of study include the epidemiological and statistical capabilities at AZHQ and Southwest Environmental Health Science Center (SWEHSC), and their datasets describing the health characteristics and treatment outcomes of patients throughout Arizona.

- **Improving the definition, diagnosis and approach to treatment of asthma through "biosignature" research.** The field of asthma research would benefit significantly from identifying specific biosignatures that indicate susceptibility or presence of the disease. Focus should be placed on the identification of cellular or molecular targets for preemptive and pre-symptomatic intervention. A related goal is identification of biosignatures specific to the affected organ (e.g., lung). Taken together, this information could facilitate the development of methods for transforming the lungs with specific therapeutic targets to decrease susceptibility to asthma. Such knowledge could also be useful in identifying common disease mechanisms of immunological responses in other disease such as arthritis and type I diabetes.

  Pursuing biosignature research in asthma would:

  - Enable a more rigorous and in-depth definition of the disease and its related manifestations;
  - Provide a systematic approach to diagnosing the disease; and

- Better link the type of asthma in a patient to treatment.

Through efforts at Arizona State University, U of A, BIO5, Mayo Clinic and the Translational Genomics Research Institute (TGen), Arizona is developing a broad capacity in biosignature and molecular diagnostics research that can be leveraged in asthma-related research.

- **Advancing clinical and therapeutic approaches to asthma treatment**. Traditional clinical and therapeutic approaches to asthma treatment have largely focused on identification and control of symptoms. Arizona possesses excellent clinical expertise but this expertise requires a source of distinction. A focus on presymptomatic and preventive medicine, rather than on "managing the symptoms," would set Arizona's clinical approach to asthma treatment apart from those of other asthma research and treatment programs. Such a focus would require a strong understanding of the immunological and genetic factors that cause the disease, not just its symptoms.

  Therapeutic research should include studies of molecular targets such as cytokines, MHC types and growth factors, and of specific cell types (T Regulatory cells) that play a role in the development of asthma symptoms.

II. Identified Assets and Gaps for Advancing the Asthma Research Platform

Arizona offers a strong tradition of asthma research that has culminated with a Specialized Center of Research (SCOR) grant from the National Institutes of Health to researchers at the University of Arizona to study respiratory disease as well as significant clinical strengths across the state. The key issue for advancing asthma research in Arizona is how to position the state as a national leader in the new paradigm of presymptomatic understanding of the disease process and preventive interventions.

ASSETS

Assets directly related to asthma research and assets that can be leveraged to position Arizona's asthma research activities for national excellence in the new paradigm were identified across the asthma research platform and include:

General Strengths

- **Core research strengths**: Institutions across the state possess expertise in basic research areas that can be leveraged towards an improved understanding of human immunology and the immunological dysfunctions that lead to physiological disorders. This expertise is demonstrated by grant awards and publications in specific areas:
    - Abstracts from nearly 1700 NIH, NSF, USDA and ABRC grant awards to Arizona institutions were analyzed using Battelle's "OmniViz" software. Abstracts were sorted into clusters based on textual similarities. A cluster comprised of 51 awards linked in their focus on "lung, heart, inflammation, child, respiratory, and asthma" was identified; the cluster seemed to be part of a broader cluster grouping signifying research strength in "cardiovascular and pulmonary" fields.
    - From 2001-2005, 191 publications in the category of "cardiovascular and pulmonary" involved Arizona universities. Compared to the national average, these publications were cited 12% more frequently. However, while Arizona accounted for 1.5% of publications in each of the other research categories, it accounted for only 0.7% of the publications in "cardiovascular and respiratory." These data suggest that although Arizona publications in this field are cited more frequently than average, the number of these publications is somewhat lower than expected.

- **Top-ranked hospitals for respiratory care:** The state of Arizona has one of the nation's top respiratory clinical infrastructures. According to the 2007 *US News & World Report* Ranking of America's Best Hospitals, the Mayo Clinic Arizona in Phoenix ranked 19 nationwide for care of "respiratory disorders" and the University Medical Center in Tucson ranked 20. St. Joseph's Hospital and Medical Center in Phoenix ranked 37.

Human Immunology

- **Arizona Respiratory Center (ARC):** The asset most directly related to asthma research is the Arizona Respiratory Center (ARC) in Tucson, an internationally renowned, comprehensive Center of Excellence that combines the highest caliber of research, clinical care and teaching. Focus areas relevant to basic human immunology include studies on cellular and molecular mechanisms of asthma through the analysis of interactions between genes, the environment and the immune system. Additional key projects include studies on innate immunity in children and the influence of maternal immune system on asthma development in children. Also, studies on the effect of environmental factors on the immune system are shedding light on the underlying genetic traits that predict the severity of asthma and other respiratory diseases.
- **Influence of the environment on the immune system – studies and resources:** A key asset to the platform is the wealth of information describing the effect of environmental factors on health and the immune system:
  - **Asthma Coalition and AZHQ**: Large datasets containing information on asthma prevalence and health care encounters for children in Yuma and Maricopa counties are valuable resources for determining which environmental factors may be contributing to the disease.
  - **Tucson Children's Respiratory Study at ARC**: The ARC has been following a specific population group and collecting data on members' respiratory health for over 20 years. Among other significant findings is the determination that environmental exposure during early years may reduce the risk of developing asthma later in childhood.
  - **Inner City Asthma Study at ARC**: The relationship between environmental allergens and the severity of asthma symptoms is under investigation in this study, which has implications for how the environment might modulate the immune system.

Diagnostics

- **ARC**: The ARC, the statewide leader in asthma-related research, is actively engaged in a number of pursuits related to the identification of biomarkers specific to asthma. These biomarkers can help determine which patients will acquire the disease, how they should be treated, and how they will respond to particular treatments. Related research projects include the characterization of gene variation in healthy patients vs. patients with heart, lung or blood disease; the identification of diet, stroke and oxidative stress risk

biomarkers in Hispanics; and the measurement of exhaled gases as indicators of respiratory disease.

- **Research strengths in genomics and epigenomics:** Institutions across Arizona have significant depth and breadth in research activities focused on genetics, genomics and epigenomics. These fields are crucial to the advancement of asthma research because they can reveal genetic signatures that are linked to asthma susceptibility or that can be used to indicate the type of treatment best suited for a particular patient. Using the OmniViz analysis, Battelle identified 445 grant awards constituting 6 clusters in the field of "basic molecular and genomic sciences." This is one of several stand-out bioscience research areas in the state.
    - **Genomics-related capabilities:** There are a number of centers well-resourced for processing and analyzing the large genomic/proteomic datasets produced by Arizona institutions. These centers possess the expertise and capabilities that are needed to further the identification of asthma-specific biomarkers. TGen, the Arizona Genomics Institute, the Molecular Profiling Institute, the Genomic Analysis and Technology Core at the Arizona Research Labs (ARL) at U of A, and the BIO5 Genome Structure and Function Consortium are examples of such centers.
    - **Expertise in diagnostics:** Strengths in diagnostics development are critical to the ability to test for the presence of asthma-specific risk factors. A number of centers throughout the state possess broad capabilities in diagnostics and include the Center for Innovation in Medicine and Center for Applied NanoBioscience, both at the Biodesign Institute at ASU, and the Biological Magnetic Resonance Facility at ARL.

Environmental Health

- **SWEHSC**: This National Institute for Environmental Health Sciences (NIEHS)-funded group promotes the study of health effects of environmental agents through collaborative, interdisciplinary research. Focus areas include the mechanisms of environmental chemical toxicity, chemical chromatin interactions, and pulmonary toxicology and lung disease. Of particular interest include research on the effect of environmental toxicants on lung structure and function, and studies investigating biomarkers linked to susceptibility following exposure to occupational health hazards. The Center is affiliated with the University of Arizona College Of Pharmacy's Center for Toxicology.

Therapeutics

- **ARC:** The ARC is engaged in a program that is exploring the effect of specific botanicals as treatment for respiratory diseases. This program draws on the strengths at the U of A in natural products chemistry research.
- **Drug discovery and development**: A number of organizations throughout Arizona are dedicated to the discovery and development of innovative therapeutics. The Center for Innovation in Medicine at the Biodesign Institute merges genomics with vaccine development and a number of other approaches towards the development of new therapeutics. The Drug Discovery Initiative and Quantitative Biology Consortium, both at BIO5, TGen's Drug Development Services, and Critical Path Institute

(C-Path) also play instrumental roles in the development and testing of new drugs.

- **Systems biology research:** Researchers at Northern Arizona University have developed a sophisticated computer-based algorithm that accurately models entire signal transduction pathways between any kind of molecules and in any cell type. Further, pathways can be altered to reflect changes that result from the interaction with therapeutics, making the model particularly useful for identification and characterization of new drugs. This powerful systems biology tool could also be used to elucidate the roles of mast cells and of IgE and other molecules implicated in the onset of asthma.
- **Natural products research**: The Southwest Center for Natural Products Research & Commercialization at the U of A has established expertise in the identification and characterization of anti-cancer compounds isolated from arid land microorganisms. This expertise can be leveraged to the identification of compounds with anti-inflammatory properties.

Clinical Research

- **Clinical and Translational Science Award**: The CTSA award is a prestigious NIH planning grant awarded to Arizona. The CTSA program is the statewide organization that will be responsible for accelerating clinical research and for bringing together the key elements needed for collaborations, including biostatistics, bioinformatics and study design.
- **CARE Network**: The Childhood Asthma Research and Education (CARE) Network was established in 1999 by the National Heart, Lung and Blood Institute (NHLBI). Five clinical centers, including the U of A, and a data coordinating center were selected to participate in this research network. The goal of the CARE Network is to evaluate treatments for children with asthma.
- **Epidemiology research and resources**: One of the best-developed resources related to biomedical research is the AZHQ database. This database contains medical records from public and private sources across Arizona and can be tapped for insight into asthma incidence, symptoms, specific populations, trends, treatments and outcomes as well as to determine which patients should participate in studies. These datasets have the potential to be expanded to include number of treatments, medications used, screening for adverse drug reactions, demographic information, rare cancers and other diseases, and exposure risks. Similarly, data collected by the Asthma Coalition, and extensive (20+ years) longitudinal studies following specific population sets are a focus of the ARC, are valuable resources for understanding key determinants of asthma.

GAPS

Specific gaps were identified in key areas across the asthma research platform. These gaps were identified via committee input and comparison of Arizona with peer programs and include:

Human Immunology

- **Adult asthma researchers:** Almost unanimously, it was agreed that the state lacks strength in clinical adult asthma research. Experts in adult asthma symptoms, progression and treatment are critically needed as the incidence in adults in Arizona continues to rise. Researchers in leadership positions are especially needed.
- **Animal models of adult asthma:** While animal models of asthma exist, none display the type of lung remodeling seen in adult asthma.
- **Basic immunology researchers**: To accelerate the pace of asthma research, Arizona must address its shortage in basic immunology researchers, not only those whose focus is asthma, but also those who can play multi-disciplinary roles in support for other inflammatory disorders. Specific focus areas where there is a gap include epithelial cells, mast cells, airway smooth muscle, and T regulatory cells. Expertise in the related fields of arthritis, type I diabetes, autoimmunity and vaccine responsiveness would also strengthen the level of asthma research.
    - **Proteomics expertise**: Currently, Arizona is facing a deficit in scientists skilled in proteomic analysis. In terms of the asthma research platform, these skills are needed for the identification of key proteins involved in asthma and inflammation.

Diagnostics

- **Tissue resources**: Although the ARC has approximately 7000 tissue samples from prior asthma studies that could be leveraged towards further studies in asthma research, more samples from specific populations across the entire state are needed. Such samples should be collected using heightened standardization procedures that will allow for clearer interpretation of any microarray studies.
- **Accessible sequencing facility in Phoenix**: For the platform's biomarker-focused approach to move forward, greater access to genomics/proteomics core facilities in the Phoenix area is needed. Current facilities offering sequencing and analytical services are prohibitively expensive for outside users.

Clinical Research

- **Low presence of clinical trials:** A survey of clinicaltrials.gov, a resource considered to be a comprehensive and up-to-date listing of clinical trials sponsored by federal agencies, non-profit and corporate groups, revealed that of the 221 clinical trials directly related to asthma and currently recruiting patients, 17 involve Arizona researchers or clinicians. This number is likely to increase as the incidence of asthma rises, driving up demand for participation in trials.
- **Collaborations with private hospitals**: Improved collaboration between universities and institutes, which possess vast research capabilities, and private hospitals and clinics, which have numerous asthma cases, is

absolutely essential. In the current situation, there is very little bridging between these two types of entities. Collaboration between these entities would yield improved sharing of basic science and clinical data that could accelerate the identification of asthma-specific biomarkers.

- **More clinical time spent diagnosing and profiling asthma**: There is a shortage of pediatric beds in Arizona clinics and as a result, physicians lack the time needed to thoroughly diagnose and profile asthma cases. This results in a dearth of quality information describing symptoms, environmental factors, and treatment outcomes that are needed to help drive the corresponding basic genetic immunological research.

III. Benchmarks

The identification of "best practices," based on the analysis of benchmarks, is commonly undertaken in the corporate and financial communities as a way of improving efficiency and calibrating performance. Similarly, in considering how to grow a technology platform, analysis of benchmarks can allow one to identify and draw useful lessons from the practices of regions and institutions that are generally comparable along relevant strategic dimensions.

Lessons Learned

Several key lessons emerge from the seven benchmark case studies that can help inform how Arizona might conceive and pursue the development of a mixed-use research campus and park.

- **Generally small, niche programs involving teams of fewer than 10 PIs whose success depends on engaging leveraging broader institutional capabilities.** Successful asthma research programs demonstrate an ability to engage in interdisciplinary research by leveraging broader institutional capabilities. Often this involves the presence of both adult and pediatric pulmonary divisions, and leveraging core labs and specialized capabilities such as aerosol science, and cell adhesion and signaling.
- **Immunology as a supporting discipline.** There was consensus that immunology research is critical for advancing asthma prevention, diagnosis and treatment. Immunopharmacology and immunogenicity were also highlighted as fields that will require more attention.
- **Range of research focus areas are found in asthma research.** While there is a growing emphasis on "personalized medicine" approaches to identify genetic markers and determine predisposition, other potential focus areas are found across the benchmarks. These include the effect of the environment on genes linked to asthma, specific molecular interventions in cell receptors and inhibitors, and making antigens and adjuvants more immunogenic.
- **Clinical research partnerships.** Leading asthma research programs have access to diverse populations through clinical research partnerships and strong affiliations with local hospitals and clinics.
- **Institutional commitment and financial incentives.** Commitment of leadership to promoting a translational research and

Selected Benchmarks

- University of Texas Medical Branch
- National Jewish Medical and Research Center
- Baylor College of Medicine/Texas Children's Hospital
- University of New Mexico

interdisciplinary collaboration is crucial to advancing asthma research. Leadership should also play a role in facilitating communication between basic and clinical researchers. To back up this institutional commitment, the benchmarks also reveal the importance of having financial incentives in place to promote interdisciplinary collaborations and clinical research in asthma.

While each of the peer programs has its own unique assets and merits, Arizona should not try to "copy" any of them, but rather build upon its own assets to distinguish itself as a leader in a focused area of asthma research.

Brief Descriptions of the Benchmarks

Below is a brief thumbnail sketch of each of the benchmark organizations:

- **University of Texas Medical Branch, Galveston:** The APICS division for Allergy, Pulmonary, Immunology, Critical Care and Sleep research at UTMB is staffed by immunologists, animal model scientists, allergists, clinical pulmonologists, and an interventional bronchologist who focus on curing respiratory disorders. The program is primarily patient care-driven but 70% of faculty are funded to conduct biomedical research.

- **National Jewish Medical and Research Center, Denver:** National Jewish has been consistently ranked the No. 1 hospital for respiratory care by *US News and World Report* and is known worldwide for its research on respiratory, immune and allergic disorders. The center has over 100 faculty in the allergy and pulmonary divisions. Basic research programs include and integrated program in immunology and a program in cell biology. Other research strength areas include environmental and occupational medicine and infectious disease research.

- **Baylor College of Medicine/Texas Children's Hospital:** Baylor College of Medicine (BCM) and Texas Children's Hospital are partnered organizations that are internationally recognized for excellence in education, research and patient care. Among medical schools, BCM currently ranks No. 1 for research expenditures in biological sciences by the National Science Foundation and No. 13 for NIH funding. Texas Children's Hospital has gained widespread recognition for its breakthrough developments in the treatment of asthma, among other disorders. Specific strength areas include pediatric pulmonary medicine, public health, and allergy and immunology research.

- **University of New Mexico Medical School:** The University of New Mexico Medical School's asthma research program is supported by an NIH-funded SCOR grant, which has three project principal investigators and one laboratory principal investigator. Related research programs at the Infectious Disease and Inflammation Program surround lung immunity, lung infection vaccines and heat shock response. Another local asset is the Lovelace Respiratory Research Institute, a private biomedical research institute whose 70 PhD-level scientists are dedicated to studies of respiratory health. Specific research areas include asthma, emphysema, lung cancer, inhalation toxicology, aerosol science, inhalation drug delivery, bronchitis and allergies.

IV. Action Plan for Asthma Research

The Asthma Platform is beginning to identify a unique, integrated and focused program in asthma research that can best be served as a statewide asthma consortium. The key elements of this strategy include:

Developing a Statewide Collaborative Research Program

For the Arizona approach to be successful, the plan must bring together the knowledge of basic research, understanding of technologies (both merging and existent) and clinical research. No single institution can bring all of these strengths. In Arizona and demonstrated in other leading institutions, it is clear that asthma is a more niche focused disease area with relatively small programs that seek to leverage broader collaborations.

Arizona already is home to one of the nation's leading asthma research centers in the nation, and has significant clinical strength in asthma and a broader base of asthma researchers. Bringing all of our clinical and research strengths together can enable us to be one of the top asthma research efforts in the world and pursue specific goals that can transform the field.

This requires defining a shared statewide asthma research program that engages the broad Arizona asthma community and identifies initial pilot projects to advance its development. Such approaches have been developed in Alzheimer's and Parkinson's disease research in Arizona, and are moving forward in autism research.

Leveraging Broader Genomic and Systems Biology Strengths

What is needed in asthma research is a strong dose of application of innovative genomic and molecular diagnostic/therapeutic approaches as well as computational biology approaches to develop models of asthma disease process. Arizona is now a national player in this arena with the investments made in TGen, ASU's Biodesign Institute, U of A's BIO5 Institute and a variety of genomics efforts at NAU.

The applications of these existing genomic strengths in Arizona need to be coupled with active biospecimen and tissue resource development. Currently the Arizona Respiratory Center has some 7000 tissue samples (blood, nasal washes and sputum) from prior asthma studies that could be leveraged towards further studies in asthma research. But a more standardized biospecimen and tissue collection effort is needed for genomic studies to be useful. This biospecimen and tissue collection

needs to be linked to serotyping (identification of cases that will allow us to know what the different symptoms and characteristics of individuals), which in effect will allow that individual to be a part of a future study. Using these samples could lead to additional discoveries and the identification of new immunological pathways involve in the symptoms of asthma.

There is also a need for intensive samples from patients (patient description, symptoms, and encounter data) and extensive samples of a population, and the ability to identify them. The ARC has reported on 10 genes from a childhood study. What is needed to further studies with tissues is to be able to identify more patients from the population. Again this begs the issue of utilizing the resources at AZHQ.

Enhance Immunology in Arizona

For asthma research in Arizona to take a major leap forward and transform the asthma research field, there is a critical need to deepen the state's human immunology resources.

Much of the investment needed in human immunology comes down to people. Arizona requires human immunology researchers that support asthma research, but can also play multi-disciplinary roles in their support for other immunological disorders.

An initial ramp up and continued steady investment in human immunology is required with the goal of having 15 to 20 leading human immunology researchers in Arizona over the next 5 years.

Preliminary discussions suggest that the specific type of human immunological researcher teams that are needed include expertise in:

- Epithelial cells: In asthma, the bronchial epithelium is modified. An epithelial cell immunologist is needed to address the mechanisms involved in cell disruption and also to explore how allergens and viruses exacerbate the lining of the lung, causing long-term respiratory distress.
- Smooth muscle cell: Increased proliferation of airway smooth muscle cells is associated with asthma. This proliferation leads to constriction of the airways. Research is needed to advance our understanding of molecular pathways that are activated in these cells in response to specific triggers. The development of asthma therapies targeting airway smooth muscle is also critical.
- Mast cells: Mast cells play a central role in the inflammation, hyperresponsiveness and remodeling of airways. Improved understanding of how mast cells trigger these events could lead to the identification of molecular targets and development of therapeutics for preventing or treating asthma symptoms.

- T regulatory cells: These cells are key regulators of immunologic processes. Evidence suggests that individuals with allergies and asthma may have malfunctioning T regulatory cells. Thus, these cell types are widely believed to carry therapeutic potential for asthma, allergies, and other inflammatory disorders.

Arizona's ability to attract leading human immunology researchers also requires advancing the availability of start-up packages and equipment and facilities. Additional areas of investment noted by the committee were in the area of supporting infrastructure and technology such as:

- A human immunology core lab comprised of:
  - Flow cytometers
  - Assays for antibody responses, cytokine-based T cell assays, MHC tetramers, secreted cytokines
  - "Immune Imaging" capabilities: high resolution scanning facilities for studying events at the cellular level
  - "Small Molecule Immune Discovery" core: high-throughput screening capabilities for rapidly identifying molecules with desirable features
  - "Immune Modulation Discovery" core: Modeling capabilities for the rational design of molecules that interact with drug targets or immune system modulators
  - Standardized methods for evaluating immune function in humans and in animal models
- Animal models of asthma
- HPLC for proteomics (High Performance Liquid Chromatography)
- Luminex or similar bioassay system

Strengthening Clinical Research Linkages

Arizona also needs to broaden its clinical research programs in asthma. We need to have a world-class capacity to not only advance innovative presymptomatic diagnostics and preventive treatments, but to test them. Today Arizona is not a leader in asthma-related clinical trials capacity.

Clinical research excellence goes hand-in-hand with overall clinical excellence. While Arizona has strong hospital-based respiratory clinical care, there are a number of key investments identified to further develop and ensure the state's strength in clinical research:

- Hire a specialist in adult asthma treatment
- Advance residency programs in asthma-related fields with a strong emphasis on clinical research.
- Develop methods and principles for teaching translational research to faculty and staff.

CRITICAL FIRST STEPS

The most difficult steps towards success are the first ones. These can set the stage for success even if they seem small in retrospect. The success of establishing the proposed integrated, translational research campus depends on at least three critical initial activities:

1) Formation of Arizona Asthma Consortium
2) Identification of Pilot Projects
3) Pursuing funding opportunities for interdisciplinary projects, such as from ABRC, NIH Roadmap, foundations