Translational Medicine Approaches to the Study of Pulmonary Diseases

Translating airway biomarker information into practice: From theoretical science to applied medicine

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ABSTRACT

Biomarkers ranging from simple to sophisticated have been used by man for many years of his existence. The main use for biomarkers over that time has been to assess relative states health and well-being, including the presence of functional limitations that presage debilitation and even death. In recent years, there has been intense interest in the development of non-invasive biomarkers to accurately predict disease state and progression, as well as potential drug therapy to assist in early mitigation of morbidity and possibly, forestall premature mortality. The development of biomarkers of airway status has followed a similar pattern, and in recent years, several biomarkers have followed the progression from basic and pre-clinical development, to clinical/translational application, and finally to potential clinical therapeutic application. Inherent in this progression is the refinement of technology that has allowed measurement of these biomarkers in a fast, convenient, and reliable fashion, such that they can be obtainable within a clinical practice setting, to allow the physician to make treatment decisions for diseases such as asthma and COPD. While the clinical therapeutic application of airway biomarkers such as exhaled nitric oxide and β_2-adrenoreceptor Arg-16 polymorphism are still in their infancy, they have followed this common pathway of development, and now will require some years of application to demonstrate their true utility as predictive biomarkers of airway status and treatment response.

1. Introduction

A biomarker has been defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention." [1]. This definition is now over ten years old; while still relevant, biomarkers have become the object of much attention and interest in recent years, and their definitions have undergone re-interpretive analysis and expansion to include variables from the simple to the complex. An important part of this recent broadening of scope has been the realization that, biomarker capabilities, i.e., the ability to be easily measured and to indicate something of value, are reliant on technological developments and breakthroughs that allow their application in situations in which other measurements may be impractical or unobtainable. It is also important to note, that under its broadest consideration, biomarkers have been utilized throughout man's history to discern states of being or even chemical reactions within the human body and other living things. As will be discussed, in many cases, those simple or more primitive biomarkers rely on simple visual or tactile assessment, needing no sophisticated measuring devices to provide a rough quantitation of the state in question. Recent technological advances have allow us to extend our understanding of bodily processes and disease states such that some measurements can now be simply performed inexpensively, in a clinical office setting, or even in the home.

One specific target of clinical and scientific interest has been the assessment of states of the airways under a variety of conditions and diseases. Given that the airways are part of a vital and dynamic system that is under neurohumoral control and can be influenced by both external stimuli and ongoing states of disease, it is easy to understand that reliable measures of lung function and status would be desirable. However, the airways and lung tissue are not easily sampled in a living human, particularly those individuals with airway disease. As such, the development of techniques to measure non-invasive or minimally-invasive airway biomarkers has become a potentially important facet of airway disease evaluation and treatment. Thus, in this article, a historical perspective on biomarkers and their development is followed, from more primitive biomarkers, to more recent and sophisticated biomarkers,

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with specific focus on recently developed airway biomarkers, some of which have allowed the translation of theoretical and basic science to direct applications in clinical medicine. This approach will illustrate the essential path that airway biomarker development has taken in several cases, serving as a model for development of additional airway biomarkers that may form the basis of future therapeutic approaches in the treatment of airway diseases, such as asthma and COPD.

2. A historical perspective on biomarkers

2.1. Primitive biomarkers

As espoused by Aristoteles (Aristotle) prior to 322 B.C., movement, with particular reference to self-generated movement, is a quality almost uniquely attributable to living beings [2,3], and has reliably been an obvious primitive biomarker of life. Man is no exception, and has used the presence and perception of simple movement of the human body to indicate life, while stillness of prolonged duration has been equated with death. While this movement refers to many aspects of limb, head, and facial movement, the presence of breathing motion of the thorax has long been taken as a reliable indicator of life. In fact, breath and breathing have been equated with life since ancient times, to the point that inhalation has been considered as an active process resultant of life forces and vitality, with exhalation being considered passive, but both being part of a never-ending cyclical process similar to a yin and yan relationship [4]. It has also been known for many years that warm breath blown onto a cold metal surface can produce condensate, due to the presence of water within the exhaled gas of mammals, including humans. Ancient writings of the Vikings from the 10th Century acknowledge this fact [5], such that breath condensation on the metal of a cold sword could be visualized [6], and interestingly, presages the current method of exhaled breath condensate collection. In the context of a biomarker for presence or absence of life, one could easily envision this application on the ancient battlefield, when breathing movements in the prone wounded soldier might become quite shallow and difficult to discern, and thus, a mist created on a sword placed beneath the nostrils of the fallen soldier could have been taken as a reliable biomarker of life. The above examples indicate that man has been able to rely on perception of movement, breathing, and simple physical chemistry as primitive, but reliable, biomarkers of life, for years throughout history.

2.2. Classical non-invasive biomarkers

2.2.1. Cyanotic and skin color biomarkers

Among the classical non-invasive biomarkers is external skin color, or its absence, in certain specific areas or structures of the body. Many examples are evident on a daily basis, but oftentimes we do not think of them in this fashion. Blue lips and fingernail beds are taken to indicate "cyanosis" due to increased de-oxy-hemoglobin levels, consistent with the color change from bright red to a deeper red with removal of oxygen from hemoglobin, which when viewed through the skin, imparts a cyan hue. Thus, a simple color change in an internally-distributed pigment like hemoglobin can indicate a general body status in a non-invasive fashion, and may indicate pathology, such as in the case of Raynaud's Syndrome [7]. Clinically, this is the concept behind identification of cyanotic "blue-baby" and is readily taken as an indication of the lack of adequacy of oxygenation in a new-born [8]. Similarly, a flushing of red within the skin of the face, ears, or near areas of increased temperature, injury, abrasion, or disease can indicate a strong local vasodilation of arterial vascular beds beneath the

epidermis [9–11], again in this case the coloration change due to the presence of oxy-hemoglobin pigment in locally high quantities. By the same token, a blanching or absence of color in the skin can indicate a strong vasoconstriction, and in this case an absence of blood in a given location is the tell-tale sign. Furthermore, physicians often use pressure applied to the fingertips to determine the relative fill-time, i.e., the time it takes for blood-associated color to return to the skin, as an easily assessable indication of circulatory health [12]. Another example of a pigment-related biomarker, a deepening in skin color can indicate recent sun exposure and the skin's protective response to it, with production of increased amounts of the biomarker pigment melanin, as evidence of this process. Another example of overall skin yellowing or color darkening, is that which occurs with increased circulating levels of bilirubin, again a pigment, which can be indicative of liver malfunction in neonates, and advanced liver disease in adults [13,14]. All of the examples referred to above rely only on simple external visual cues, and no measurement devices, save the human eye and brain, for their quick and reliable assessment. Being at the extreme end of non-invasive, these biomarkers give only global assessments, and do little to quantify or compare magnitude within or across individuals.

2.2.2. External electrical skin potentials

There are a number of classical biomarkers that require simple electrical sensors and are non-invasive, in that measurements are taken on the skin, without penetration, essentially treating the body as a battery that generates potential differences, measurable using connection points widely distributed across the surface. The electrocardiogram (ECG) is an excellent example of a classical non-invasive biomarker of heart activity and health, measured in this fashion. Indeed, the measurement of these electrical skin potentials has become a standard assessment used clinically for years, with remarkable accuracy even down to the indication of pathology and its probable location within the heart. For example, ventricular bundle branch blocks and SA node misfiring can be readily diagnosed with this simple tool requiring no cavity or organ penetration [15,16]. A similar example is the electro-encephalogram (EEG), an indicator of brain activity due to potentials measured on the scalp and forehead. These non-invasive recordings have patterns consistent with known levels of neural activity during activities such as wakefulness, arousal, and certain emotional states. The EEG is a staple of clinical sleep studies as well, in which the EEG pattern can readily indicate the various stages of sleep, that are quantifiable in difference and duration, allowing the physician to assess the relative quality of sleep in an individual.

Thus, while there are many more examples, external color indicators due to pigments in or beneath the skin, and measurement of simple electrical potentials on the skin, are two easily appreciated and familiar biomarkers still in use today. However, with increased sophistication over years of man's history, more recently developed biomarkers have come into use, and have been helpful in clinical practice and therapy.

2.3. Recently developed biomarkers

In more recent times, and in the broadest sense of biomarkers as outlined above, man has developed and utilized more sophisticated biomarkers to aid in the diagnosis and treatment of disease, both in an effort to increase scientific and clinical knowledge, and to alleviate pain and suffering. In the mid-1900s, emphasis was placed on biomarker development utilizing clinical chemistry approaches that were mainly applied within hospital clinical laboratories. Some of these included integration of light microscopy and dyes at the cellular level, such as simplified