thorough history and physical examination, recognized patterns of HRCT images obtained with proper technique and in both inspiration and exhalation (1), broad serological testing, BAL cellular profile, consultation with a rheumatologist, and an MDD can yield the specific diagnosis of ILD without subjecting patients to the risks of invasive procedures to obtain lung biopsy for diagnostic interventions. ■

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# Harnessing Immune Response to Malignant Lung Nodules
## Promise and Challenges

Incidental and screen-detected lung nodules are a common problem (1) and one that is driving the search for diagnostic biomarkers that can distinguish malignant from benign lung nodules with acceptable accuracy. Many investigators are pursuing this line of work, and the importance of this pursuit is increasing, in part because of the increasing adoption of lung cancer screening. The vast majority of indeterminate lung nodules discovered incidentally or in the context of lung cancer screening are not cancer (2, 3). Nevertheless, many patients with benign lung nodules may undergo unnecessary and invasive diagnostic procedures. Standard computed tomography (CT) imaging lacks the ability to accurately differentiate between malignant and benign lung nodules. Although positron emission tomography scans have a very good negative predictive value, their use is limited for smaller nodules; there is a high (>20%) risk of false-positive findings,

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which lead to increased cost and risk to the patient (4). There remains a crucial and unmet clinical need for biomarkers that can distinguish malignant from benign lung nodules with sufficient accuracy to be clinically useful. Blood-based biomarkers represent a promising approach in the diagnosis of indeterminate lung nodules if we can identify biomarkers with a high negative predictive value for cancer.

In this issue of the *Journal*, Lastwika and colleagues (pp. 1257–1266) address whether tumor-associated autoantibodies can distinguish between malignant and benign lung nodules identified by CT imaging (5). Autoantibodies have attracted interest as potential biomarkers for early diagnosis, as the occurrence of autoantibodies has been found to precede clinical diagnosis by several months to years (6). These investigators sought to identify tumor-associated autoantibodies by isolating tumor-infiltrating B cells and profiling IgG and IgM autoantibodies in their extracts. Antigens were identified by overlaying B-cell extracts on a human proteome array that contains 17,000 yeast-produced human proteins, covering approximately 80% of the human proteome. Matching plasma samples from the same patients were also overlaid on a human proteome array to determine which tumor-associated autoantibodies could be simultaneously detected in circulation. Interestingly, 56% of autoantibodies identified in lung tumor–infiltrating B cells were also identified in the plasma from the same patients, suggesting that autoantibody profiles in blood actually reflect immune response of B cells in the tumor microenvironment.

Next, they tested whether tumor-associated autoantibodies existed as free or complexed with antigens in plasma, by creating a custom antibody array using commercially available antibodies to the 13 antigens of interest. Importantly, they found that the levels of antigen-antibody complex for a set of autoantibodies were significantly higher in plasma of subjects with malignant lung nodules compared with plasma from subjects with benign lung nodules. The results suggest that circulating antigen-antibody complexes and free autoantibody may both act as diagnostic biomarkers and reflect the host immune response to tumor.

The authors validated the occurrence of autoantibodies against five antigens in the form of either free autoantibodies or antigen-antibody complex in an independent validation set consisting of 250 plasma samples from subjects with lung nodules (50% malignant, 50% benign). A logistic regression model of four autoantibodies (FCGR2A, EPB41L3, and LINGO1 IgG-complexed autoantibodies and S100A7L2 IgM-complexed autoantibody) yielded an area under the curve of 0.737 (33.3% sensitivity at 90% specificity). Of note, the performance of this four-autoantibody panel had an area under the curve of 0.779 (91.7% sensitivity at 57.1% specificity) in indeterminate lung nodules of 8- to 20-mm size. This finding is critical, as it is in subjects with nodules in this size range where diagnostic biomarkers have the greatest potential for clinical impact.

The authors have described a novel approach to identify autoantibodies from tumor-infiltrating B cells and simultaneously identified a set of promising tumor-associated autoantibodies. They have further demonstrated the potential value of circulating autoantibodies both in free form and complexed to their antigens. There are some limitations to this study. First, an optimal biomarker-based model with sufficient performance to meet the requirements for clinical applications will require comparing the relative contribution of different types of biomarkers and integrating those with complementary nature to distinguish malignant from benign lung nodules. These include biomarkers like microRNA (7, 8), protein (9), or other autoantibodies (10). A study that assesses the relative contribution of each of these will be complex and likely very expensive. Second, as the cases and control subjects in this study were matched on sex, age, and pack-years, the authors could not compare the performance of autoantibodies with established clinical risk prediction models using radiographic biomarkers as well as demographic data (11–13). Further validation of this approach would require an unmatched cohort.

It is fair to ask what impact this study will have on the search for effective biomarkers. In this light, a committee from the Assembly on Thoracic Oncology of the American Thoracic Society met in 2017 to consider the metrics by which the utility of a biomarker might be judged. The resulting report was a framework on which to consider the potential for a given biomarker to impact management of a nodule in a defined clinical application (14). This guidance suggests that a "rule in" biomarker (for instance) would need to have to perform significantly better (sensitivity and specificity) than this candidate panel currently does, but these authors have to be recognized for the novel approach they have defined in identifying potentially useful tumor-associated autoantibodies. If the search for biomarkers can be viewed as analogous to a fishing expedition, then Lastwika and colleagues have not only caught some potentially new fish but also may have found a new type of fishing pole. ■

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# Pharmacotherapy of Obstructive Sleep Apnea: Is Salvation Just Around a Corner?

Obstructive sleep apnea (OSA) is recurrent upper airway obstruction caused by a loss of upper airway muscle tone during sleep, which leads to intermittent hypoxia and sleep fragmentation (1). OSA is a common disorder affecting 25–30% of the adult population, and more than 50% of obese individuals (2). Continuous positive airway pressure (CPAP) relieves OSA, but poor adherence severely limits its use (3). Mandibular advancement devices have better compliance, but are not as effective as CPAP (4). There is no effective pharmacotherapy.

Successful drug development is possible only when the pathogenesis of the disease is fully understood. Four key pathophysiological mechanisms of OSA have been identified: anatomically compromised or collapsible upper airway, inadequate compensatory responses of the upper airway dilator muscles during sleep, a low arousal threshold, and an overly sensitive ventilatory control drive (5). Anatomic predisposition plays a primary role in OSA pathogenesis (6), whereas faulty neuromuscular mechanisms during sleep fail to compensate adequately for compromised pharyngeal patency (7).

The tongue plays a critical role in the pathogenesis of OSA and has been targeted for therapy (8). The upper airway patency is regulated by lingual protrudors, including the biggest upper airway dilator, the genioglossus (GG) muscle. Hypoglossal nerve electrical stimulation has been effective in activation of the GG muscle and relieving OSA in a subpopulation of patients intolerant of CPAP, but it is invasive (8). Until now, pharmacological approach did not reveal drug candidates, which effectively restore pharyngeal patency and treat OSA (9, 10).

Multiple potential targets on hypoglossal motoneurons have been identified, but until now translational studies either failed or had limited success (9). Serotonin (5-hydroxytryptamine) exerts excitatory effects on hypoglossal motoneurons, and withdrawal of serotonergic mechanisms has been previously considered as the main mechanism for loss of neuromuscular input during sleep (11). However, "the serotonin hypothesis" has been downplayed, because activation of serotonergic mechanisms had limited success in preclinical models (12) and clinical trials (13).

Subsequent studies from Horner's laboratory proposed distinct mechanisms of hypoglossal motor pool activation during non-REM (NREM) and REM sleep (14, 15). The investigators examined the role of an endogenous noradrenergic drive in maintaining GG muscle tone during sleep in rats. Microdialysis perfusion of the $\alpha$1 receptor antagonist terazosin into the hypoglossal nucleus decreased GG activity, whereas the $\alpha$1 receptor agonist phenylephrine increased GG activity during wakefulness and NREM sleep, but not REM sleep (14). The same group demonstrated that GG muscle tone in REM sleep is regulated by muscarinic receptors with a significant increase in GG muscle tone by muscarinic blockers without pronounced effects during wakefulness and NREM sleep (15).

This experimental work laid a foundation for a phase 1 clinical trial of desipramine (9), a tricyclic antidepressant blocking norepinephrine reuptake. Desipramine reduced pharyngeal collapsibility (Pcrit), but it had a very limited effect on the main marker of OSA severity, apnea–hypopnea index (AHI).

In this issue of the *Journal*, Taranto-Montemurro and colleagues (pp. 1267–1276) (16) reasoned, based on this experimental work, that a combination of norepinephrine reuptake inhibitor and muscarinic blocker may optimally modulate the GG muscle tone across sleep stages. The investigators performed a one-night randomized placebo-controlled double-blind crossover trial of a fixed dose of a norepinephrine reuptake inhibitor atomoxetine and an antimuscarinic drug oxybutynin, which they named ato–oxy.

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