**Seminar Report #2**

**Ian Linville**

***The Genetics and Pharmacogenetics of Idiopathic Pulmonary Fibrosis (IPF): the role of TOLLIP***

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Pinn 1017

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This presentation was about Idiopathic pulmonary fibrosis (IPF), a chronic disease that causes fibrosis of the lungs with an unknown cause. In the lungs it presents itself in a honeycomb pattern and causes the lungs to thicken and make it harder to breathe. Currently the 5 year survival rate is at 30-50% and there are about 50,000 cases a year. IPF is heterogeneous in its natural history, non-predictable and is largely based on the genetics of the individuals. It has comorbidities that often cause death, such as congestive heart failure or pulmonary embolisms.

Noth proceeded to discuss TOLLIP, a toll interactive protein, that has canonical negative regulation of TLR at Myd88 and TIRAP signaling pathways. Following TOLLIP he discussed the PANTHER study that gave IPF patients prednisone, azathioprine, and NAC. The results of this study discovered that taking all three increased the likelihood of dying by almost 9X, but it led to a study of just NAC that seemed to have secondary effects. They did a genotype count and compared using a Chi-square test and then continued to test the drug-gene interaction with multivariable cox regression models. This study concluded that NAC is only effective in about 1 out of 4 patients, being related to the individual’s genetics.

Then they studied the mechanisms of NAC in the TOLLIP variants, and concluded that antioxidant NAC effectively eliminated inflammatory signals in excess TOLLIP. But once again, it was extremely important to know the individual's genetics because if you take NAC with the wrong genotype it can actually make it worse. They’re now working on getting a prospective treatment in ipf using genotypes for NAC selection, with about 1000 patients and have identified 40-60% of the genes associated in these processes. Once more genes have been identified it should help more with prognosis of IPF. It is still not fully understood, but currently they are attempting to identify more targets and mechanisms associated with IPF.

One question I had is how they would be able to determine who would be able to get these treatments if ever produced in larger quantities. Since it is only effective with certain genetics, and can cause even more damage with different genetics, would everyone have to have their DNA mandatorily tested? This is a really limiting factor in the distribution of this treatment. Another question I had was about the disease in general. If it is so unpredictable, and the initial symptoms are simply shortness of breath. What ways have they been able to diagnose these early? How often is this misdiagnosed and let to increase over time? Are there any tactics they have besides a full CT to catch this diagnosis?

**Seminar Notes:**

Idiopathic pulmonary Fibrosis

* Chronic fibrosing lung disease of unknown cause
  + No exposure to fibrosing agents
  + No systematic illness
* UIP pattern
  + HRCT with UIP pattern
  + Surgical lung biopsy with UIP Pattern
* 5 year survival rate is 30-50%
* Two approved pharmacological treatments
* Its a SYNDROME not molecular
  + As the lungs get smaller, it gets harder to breathe, similar to a thick/thin balloon thick is harder.
* Honeycomb pattern on the lung ct = UIP

Differential Diagnosis

* Other idiotpathic interstitial pneumonias
  + - NSIP
    - DIP
    - RB-ILD
    - AIP
    - COP
  + Connective tissue disordres
  + Asbestosis
  + Hypersensitivity pneumonitis
  + Sarcoidosis
  + Chronic Drug Toxicity
  + Other Diseases: COPD, CHF, Lymphangitic CA.
* IPF has a heterogeneuous natural history
  + It is not predictable
  + You never know what its going to do, it could kill you or it could last years.
  + Based on the individual
    - Genetic predisposition
* IPF comorbidities:
  + Obstructive sleep apnea
  + Reflux
  + Pulmonary hypertension
  + Chronic obstructive pulmonary disease
  + Depression
  + Pulmonary embolism
  + Congestive heart failure
  + Shows up originally with a harder time breathing
    - Not sure if its a singular disease or a combination of multiple
* Conceptual Model
  + Environment/Injury
    - I.e: Tobacco, toxins, infection etc
      * Injury and impaired repair epithelial injryAge, Genetics
  + Adjusted Event Free Survival Curves
    - Stratified presence of Staph and Strep
* Current NIH Trial with 500 patients
  + Way ahead of schedule
    - Before/After antibiotics in a year
* Telomere shortening is involved as well.
  + Carriers also carry short telmeres
* What is TOLLIP
  + Toll interactive protein
    - Canonical negative regulation of TLR stimulation at the Myd88, and TIRAP signaling pathways
* PANTHER study
  + IPF patients aged 35-86 years
  + Prednisone, azathioprine, and NAC
  + If you took all three it increased the risk of dying almost 9 fold.
  + Their testing was hurting people more.
    - NAC alone, seemed like it had a secondary effect
  + NAC vs Placebo
    - It seems like its effective, but the post doesnt, so it averages out to look about the same.
    - Collection of DNA in the study was only half
  + Failed to meet the genomic significance
* Methods
  + Genotype counts/frequencies compared using Chi-square or fishers
  + Drug gene interaction with multivariable cox regression model
  + Composite endpoint used
* Results
  + Numbers are too small
  + Only took the 50%
  + New study says only given the DNA
  + Drug Gene interaction
    - Rs3750920
    - Significant between NAC and (TOLLIP)
    - Suggested interaction between NAC and rs5743894
  + Replicated
    - Homozygous minor = hazard 5x better
    - Homozygous majore = 3x more to do bad
    - Heterozyg = neutral
* Conclusions
  + NAC is effective in about ¼ patients
  + First pharm interaction in treatment of IPF
  + No clinical trait differences noted between genotyped and not genotyped
* Potential Mechanism of NAC in setting of TOLLIP variants
  + LPS involved alternative splicing results in the induction of TOLLIP iso5 expression
  + TOLLIP iso5 expressing involved inflammation is due to
  + Antioxidant NAC effectively eliminated inflammatory signals in excess TOLLIP iso5
    - Break on the signal transduction on the toll receptor
* If you take NAC with the wrong genotype it can make it worse, but if its the right genotype it can help.
  + YOU HAVE TO KNOW what DNA they have because you can end up causing death
    - Question: How do you help plan for mass marketing of something like this for rollout?
    - NAC Is primary treatment for tylenol overdoses
* Prospective treatment efficacy in ipdf using genotype for Nac selection (PRECISIONS TRIAL)
  + Randomized, double blinded, phase III multicenter clinical trial of N-acetylcysteine in idopathic pulmonary fibrosis
  + At 1000 IPF patients
* Summary
  + 40-60% identified genetics
  + SHould help with prognosis and novel targets
  + Good for mechanisms.