

Research Award:

Evaluation of alternatively spliced Th2-related genes in alveolar macrophages and bronchial epithelial cells by Frac-seq, to investigate their influence on the modulation of proteomic output and relationship to disease severity in asthma.

Awarded to: R. T. Martinez-Nunez **Amount:** £10,000

Lay summary

Asthma has a strong genetic component, but we do not fully understand its molecular mechanisms. This hinders development of more efficient drugs targeting specific molecules in the lungs of people with asthma. Genes (mRNA) contain information to produce proteins, the main functional units in the cell. Traditional scientific approaches investigate levels of genes translating them into levels of protein production. We now know this is not accurate, as genes exist in different forms (isoforms), of which only a fraction generate proteins affected by regulators called microRNAs.

I developed Frac-seq, a technique measuring isoforms bound to the cellular machinery converting mRNA into proteins (ribosomes). Those mRNAs in ribosomes are missed with conventional scientific techniques. I analysed the role of microRNAs, key regulators of protein production, applying this method and comparing airway cells from volunteers with severe asthma against healthy volunteers. This revealed new asthma-specific microRNAs influencing nearly half of the changes we detected in asthma-related isoforms. These findings would be missed without applying Frac-seq. These microRNAs are potential novel candidates for drug development. Thanks to the AAIR Charity grant I have been able to fund part of this research hoping to publish my findings soon. The AAIR Charity funds also allowed me to investigate alveolar macrophages, key guardians of our lung immune response, uncontrolled in asthma. I am investigating novel isoforms related to inflammation not responding to current treatment options.

Publications

- Martinez-Nunez R. T. , Wallace A., Coyne D., Bailey J., Jansson L., Ennajdaoui H., Rush M., Deinhardt K., Sanchez-Elsner T., Sanford J.R§. Rapamycin modulates nonsense mediated decay. doi: <http://dx.doi.org/10.1101/028332>. Manuscript acceptor in Nucleic Acids Research. I conceived, conducted and analysed experiments, as well as writing of the manuscript. I am also the corresponding author. This paper

benefited from overleft reagents purchased thanks to this grant, allowing me to explore RNA decay by mTOR signalling, of potential application in asthma in future projects.

- Martinez-Nunez R. T., Rupani H., Niranjana M., Howarth P.H., Sanchez-Elsner T. MicroRNAs underlie genome wide transcriptome and translome dysregulation in severe asthma airway epithelium. Manuscript in submission (November 2016). I conceived, conducted and analysed experiments, as well as writing of the manuscript. I am also the corresponding author. This is the main paper arising from the AAIR Charity grant.

Presentations

- Studying post-transcriptional gene regulation with Frac-seq: rapamycin modulates nonsense mediated decay and microRNAs predominantly regulate genome-wide translation in asthma. Invited Talk in London RNA Club, November 2016.
- Coordination of alternative splicing, translation and mRNA stability – all you ever wanted to know about polyribosomal mRNA sequencing – in human primary cells. DC/Macrophage Forum University of Southampton, September 2016.
- Bronchial epithelium in severe asthma shows a mismatch between transcription and translation, as revealed by RibomiR-seq. Invited Talk in University College London, hosted by Prof Rachel Chambers. May 2016.
- RibomiR-seq reveals that global microRNA binding fine-tunes the transcriptome but profoundly alters the translome in severe asthma. SouthWest RNA Club, May 2016.
- Global microRNA binding fine-tunes the transcriptome but profoundly alters the translome: the application of RibomiR-seq to the understanding of epithelial cell activation in severe asthma. 31st Symposium Collegium Internationale Allergologicum, Charleston, South Carolina, April 2016.
- RibomiR-seq reveals microRNAs fine-tune the transcriptome but profoundly alter translation in severe asthma. 14th Lung Science Conference, European Respiratory Society. Estoril, March 2016.
- CES Club, Faculty of Medicine, University of Southampton. “microRNAs and translation two sides of the same coin”. March 2015.
- Bioinformatics Journal Club, University of Southampton. “Frac-seq in asthma: RNA-seq of polyribosomes gives a new picture of disease”. January 2015.

Posters

- T. Martinez-Nunez, H. Rupani, T. Sanchez-Elsner, P.H.Howarth. Polyribosome profiling and RNA-sequencing of human primary bronchial epithelial cells reveals novel and unique signatures of severe asthma. Lung Science Conference, European Respiratory Society. Estoril, March 2015. Poster Presentation and Travel Award.
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