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| **Name** | ANDREAS WACK |
| **Position** | Senior Group Leader |
| **Year joined *(Crick or founder institute)*** | 2009 |

## Career History

1988 - Biology Diploma study programme at the University of Konstanz, G
1995 - PhD thesis with Dr. D. Kioussis at the NIMR, Mill Hill, London, UK
1999 - Post-doc position at Chiron Research Center, Siena, Italy
2003 - Senior staff at the Chiron, then Novartis Vaccines Research Center, Siena, Italy
2009 - Programme Leader, National Institute for Medical Research (NIMR), Mill Hill, London, UK
2015 - Senior Group Leader, Francis Crick Institute, London, UK

## Major Awards, Honours and Prizes

## Membership of external committees, editorial boards, review panels, SABs etc

2019 - External Review Committee member, Institut Pasteur, Lille, France

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| **Lab Name** | ***Immunoregulation Laboratory*** |

## Research programme and achievements

Acute infections and chronic inflammation in the respiratory tract remain among the leading causes of morbidity and death worldwide. In a vicious circle, chronic inflammatory lung conditions such as chronic obstructive pulmonary disease (COPD) and asthma facilitate infections, which in turn aggravate inflammation.
Lung-infecting microbes cause tissue damage that requires timely repair. The host response to infection can increase tissue damage, and can impact positively or negatively on repair processes. We study the interplay between infection, immune response, inflammation, tissue damage and repair, to understand pathogenesis and protection in lung infection.

**1. Complex effects of interferons (IFNs) in viral infection**
IFNs are prototypic antiviral cytokines. However, we showed that due to their pleiotropic functions, IFNs are not always protective but have more complex effects in viral infection. Type I IFNs (IFN-α□and□IFN-β) drive inflammation, CCL2-dependent monocyte recruitment and airway damage early during influenza, while type III IFNs (IFN-λ) do not

have these proinflammatory properties. In contrast, late in infection IFN-λ impairs epithelial proliferation and differentiation, thus delaying tissue repair, an effect that is less evident for IFN–α and□□β. We demonstrated that unregulated IFN responses not only increase influenza severity but also facilitate bacterial superinfection, a common complication of influenza today, and observed in >95% of biopsies tested from victims of the 1918 influenza pandemic which claimed an estimated 50 million deaths. Therefore, tight IFN regulation is crucial, and we test whether drugs can be repurposed to harness IFN-mediated protection and limit IFN-driven pathology. Our studies extend beyond the above areas and have obvious clinical relevance to identify host-directed treatment options for known and novel respiratory viruses.

**2. Long-term changes to lung immunity by self-limited influenza infection**
Influenza yearly infects 8-15% of the world population, and most people survive infection. We found that influenza leaves a lung imprint beyond recovery, with long-term changes in lung immunity in post-influenza mice. Post-influenza immune reactivity is increased due to newly recruited, monocyte-derived cells that contribute to the pool of alveolar macrophages, while self-renewing tissue-resident macrophages that are hyporesponsive remain unchanged. Newly recruited macrophages slowly change over time of residence in the recovering lung, to become eventually as hyporesponsive as resident alveolar macrophages.

We envisage that origin and residence time in the lung are major determinants of macrophage function, with the (inflamed or uninflamed) lung environment further impacting on macrophage responsiveness. We plan to investigate the mechanisms underlying the slow change from hyperresponsive to hyporesponsive lung macrophages. Given that macrophage reactivity is important in cancer and chronic inflammation in the human lung, we are using our mouse dataset to identify surface markers that indicate the origins of human macrophages: monocyte-derived recruited versus embryonic-derived tissue-resident alveolar macrophages.

Another candidate for influenza-induced long-term changes are lung epithelia, as epithelial precursors reside locally and can potentially be imprinted. As epigenetic changes to lung epithelia are known to be central to COPD, we have started investigating whether there is also epithelial memory of prior lung infections.

**3. Airway epithelial cells (AECs): Conditions for (re-)development and repair**
Airway epithelia are targeted by pathogens, trigger early immune responses, and need to be intact to ensure organ function. Correct epithelial repair is an important determinant of recovery from infection, and incorrectly differentiated airways are a hallmark of COPD. In many organs, metabolism co-determines cellular differentiation, and metabolic alterations contribute to pathogenesis. We have followed metabolic changes during lung epithelial differentiation and find that a switch to fatty acid oxidation is required for differentiation *in vitro* and *in vivo*. We have previously described that the aryl hydrocarbon receptor (AhR), known as a sensor of pollutants and toxins, orchestrates development of multiciliated cells in airway epithelia. We now find that AhR has an important role in limiting epithelial damage during viral infection, and we are currently investigating if AhR also affects metabolic rewiring of epithelia, as suggested in other cell types. Fam13a, the most consistent COPD GWAS hit, has been implicated in regulating fatty acid oxidation in epithelia, and we are testing the hypothesis that Fam13a contributes to COPD through epithelial dysfunction due to metabolic alterations.

To summarise, the integrated analysis of lung immune responses and epithelial differentiation will take our understanding of infections and chronic inflammatory conditions to a new level.

## Research outputs

**Major, J., Crotta, S., Llorian, M., McCabe, T.M., Gad, H.H., Priestnall, S.L., Hartmann, R. & Wack, A. (2020) *Type I and III interferons disrupt lung epithelial repair during recovery from viral infection*. Science 369(6504):712-717. DOI: 10.1126/science.abc2061.**
We showed that interferons (IFNs), known to have antiviral effect, can aggravate respiratory viral infection if present late during infection when epithelial repair sets in. IFN-β and, most potently, IFN-λ reduce airway epithelial proliferation and differentiation in that recovery phase. This is important to understand the complex roles of IFNs in viral infections and has important implications for IFN treatments as presently discussed for COVID-19.

**Aegerter, H., Kulikauskaite, J., Crotta, S., Patel, H., Kelly, G., Hessel, E.M., Mack, M., Beinke, S. & Wack, A. (2020) *Influenza-induced monocyte-derived alveolar macrophages confer prolonged antibacterial protection*. Nature Immunology 21(2):145-157. DOI: 10.1038/s41590-019-0568-x**
We found long-lasting changes in lung immunity 28 days after influenza infection in alveolar macrophages (AMs), a population that in naïve mice is embryonically derived and self-renewing. Post influenza, cells derived from monocytes recruited early during influenza contribute to the AM pool. They are indistinguishable from embryonically derived AM by surface phenotype, but show a functional, transcriptomic and chromatin profile more similar to blood monocytes. Hence, the changed functionality is due to the changed composition of the pool of AMs. The AM population in humans will likely be a mosaic of cells recruited at different times with different functionalities.

**Bradley, K.C., Finsterbusch, K., Schnepf, D., Crotta, S., Davidson, S., Fuchs, S.Y., Staeheli, P. & Wack, A. (2019) *Microbiota-driven tonic IFN signals in lung epithelial cells protect from influenza infection*. Cell Reports 28, 245-256. DOI: 10.1016/j.celrep.2019.05.105**
This study showed that gut microbiota help maintain the IFN signature in lung epithelia and thus contribute to antiviral protection. Antibiotic-treated mice show a reduction in the IFN signature in lung epithelia, the main target of influenza virus infection, leading to increased virus replication in these cells as early as eight hours post infection. The study has important clinical implications and for livestock farming, indicating that antibiotic treatment of healthy organisms likely increases susceptibility to respiratory viral infections.

**Villa, M., Crotta, S., Dingwell, K.S., Hirst, E.M.A., Gialitakis, M., Ahlfors, H., Smith, J.C., Stockinger, B. & Wack, A. (2016) *The aryl hydrocarbon receptor controls cyclin O to promote epithelial multiciliogenesis*. Nature Communications 7, 12652. DOI: 10.1038/ncomms12652**
The aryl hydrocarbon receptor (AhR) has physiological roles at barriers and in mucosal immunology, but its roles in the lung are less well known. We showed here that AhR directly targets and induces cyclin O, a master regulator of the differentiation of multiciliated cells in airway epithelia. In the absence of AhR, multiciliated cells develop less well, with likely consequences for the mucociliary escalator mediating non-inflammatory removal of particles from the lung. Toxic ligands direct AhR away from inducing a multiciliation programme

towards activating a detoxification programme, demonstrating a molecular link between airway pollutants and lung disease.

**Davidson, S.*, McCabe, T.*, Crotta, S., Gad, H.H., Hessel, E.M., Beinke, S., Hartmann, R. & Wack, A (*equal contribution). (2016) *IFNλ is a potent anti-influenza therapeutic without the inflammatory side effects of IFNα treatment*. EMBO Mol. Med 8(9):1099-1112. DOI: 10.15252/emmm.201606413**

We have previously shown that IFNα can aggravate influenza infection by enhancing pathogenic inflammation. In a direct comparison of IFNα and IFNλ, we showed that IFNλ does not have these proinflammatory effects. IFNλ is therefore the preferred treatment option early in influenza, as the antiviral effects are similer to those of IFNα, but immunopathology is not enhanced by IFNλ. This paper suggests that IFNλ should be used for COVID-19 treatment, but early use is important (see Major et al, above).