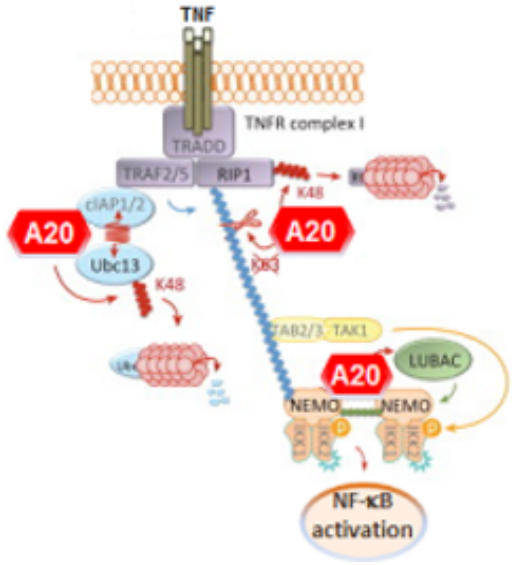
Technology Offer

# Negative regulation of the IKK/NF-kB pathway activity by stabilisation of A20 mRNA – a new approach to treat inflammation

Reference Number 03-00380

**Challenge**
Despite the emergence of novel biologics for the treatment of chronic autoinflammatory diseases such as rheumatoid arthritis, the management of these diseases does still impose a significant burden to healthcare systems worldwide. The underlying molecular causes are poorly understood and most approaches focus on neutralization of pro-inflammatory cytokines like TNF. By activation of the TNF receptor TNF acts as a potent activator of the transcription factor NF-kB which is a central mediator in inflammatory signalling pathways. Fine-tuning of this complex system is i.a. accomplished by the deubiquitinase A20 (also known as TNFAIP3) terminating TNF-mediated signalling downstream and subsequently inhibiting NF-kB signalling. A20 deficient mice develop spontaneous multi-organ inflammation and several studies reveal a clear link of A20 with rheumatoid arthritis, inflammatory bowel disease (IBD) or SLE. Notably, loss-of-function somatic mutations or polymorphisms in human A20 are associated with a variety of autoimmune diseases as a result of dysregulated NF-?B activation. Thus, stabilisation of A20 represents a novel and promising concept for the treatment of inflammatory processes.




*The role of A20 in TNF signalling*

**Technology**
Gene expression is tightly correlated with the stability of the transcribed mRNA. RNA-binding proteins (RBP) play a major role in post-transcriptional control of RNAs and regulate for instance mRNA stability by binding RNA and triggering its decay. This mechanism allows for rapid on- or off-switching of certain genes. The present technology provides antisense oligonucleotides for inhibiting the degradation of A20 mRNA resulting in attenuation of TNF signaling and NF-kB signalling. PAR-CLIP (photoactivatable-ribonucleoside-enhanced crosslinking and immunoprecipitation) experiments revealed for the first time the binding site of the RBP Roquin (also known as RC3H1) on A20 mRNA. The Roquin binding site was found on the untranslated 3'-UTR and features a distinct stem loop hairpin. Knock-down of Roquin showed a clear increase in A20 protein and subsequently a reduced NF-kB DNA-binding activity. Moreover, blocking of the Roquin binding site by a specific LNA antisense oligonucleotide resulted in a pronounced slowdown of A20 decay. In a recent study, A20 was shown to protect against arthritis by downregulation of the inflammasome. Antisense technology might therefore present an interesting treatment option.

**Commercial Opportunity**
Available for licensing or co-development

**Patent Situation**
PCT patent application pending: PCT/EP2015/070014 (priority date: 2. September 2014)

**Further Reading**
Murakawa et.al. "RC3H1 post-transcriptionally regulates A20 mRNA and modulates the activity of the IKK/NF-?B pathway", Nat. Commun. 2015, 6: 7367.
Vande Walle et.al. "Negative regulation of the NLRP3 inflammasome by A20 protects against arthritis ", Nature 2014, 512(7512), 69-73.
Shembade et.al. "A20-mediated negative regulation of canonical NF-?B signaling pathway", Immunol. Res. 2013, 57(1-3), 166-71.

MDC MAX-DELBRÜCK-CENTRUM FÜR MOLEKULARE MEDIZIN IN DER HELMHOLTZ-GEMEINSCHAFT

**Licensing Contact:**
Dr Michael Karle
Technology Manager
T: +49 30 948930-02
karle@ascenion.de

**Ascenion GmbH**
Herzogstraße 64
D-80803 München
T: +49 89 318814-0
info@ascenion.de
www.ascenion.de