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of established tumors. hetIL-15 has the unique property to increase intratumoral CD8 cells and to also increase dramatically the ratio of CD8 to Treg. We dissect the mechan- 
isms leading to tumor control in hetIL-15-treated mice, revealing a novel interplay between IL-15 and the cognate cytokine interleukin-2 (IL-2).

Repeated subcutaneous administration of purified hetIL-15 in macaques resulted in sustained plasma IL-15 levels and in dose-dependent expansion of NK and T cells in blood and tissues, demonstrating pharmacokinetics and in vivo bioactivity superior to monomeric IL-15. On the basis of these data, we have produced and characterized a cGMP preparation of hetIL-15 and we have initiated a Phase 1 dose escalation clinical trial in metastatic cancer to assess safety and activity of this cytokine.

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Regulation and B-cell help mediated by distinct subsets of IL10-producing T-cells

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IL10 is a B-cell growth factor produced by CD4+ helper T-cells, but it also medi- 
ates suppression of T-cell responses by regulatory T-cells. We found that IL10-producing 
regulatory T-cells (Tr1) and IL10-dependent B-helper T-cells are distinct subsets in 
humans and mice.

Tr1 cells that suppressed T cell proliferation and experimental colitis co-
expressed CCR5 and PD1, but not CCR6 or IL-7R. They down-regulated IL-10 produc-
tion in response to pro-inflammatory cytokines, and consequently produced only low 
levels of IL-10 in the intestine of IBD patients. Tr1 cells failed to up-regulate CD40L 
and did not promote B-cell responses, but conversely suppressed IgG production. 
However, Tr1 cells from lupus patients were unable to inhibit B cell responses.

In marked contrast, IL10-producing IL-7R+ CCR5+ helper T-cells expressed 
CD40L and induced B-cell antibody production via IL10. Notably, these IL10-depen-
dent B-helper T-cells were distinct from conventional Th17 and Th17-like cells, 
were auto-reactive and consequently provided spontaneous B cell help in lupus patients.

In summary, we defined a strategy to distinguish IL10 producing T-cell subsets 
with opposing functions in B-cell responses and in autoimmune diseases.

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Investigating the role of interferon-4A in hepatitis C virus infection

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IFN4, a recently discovered member of the interferon family (IFNIs or type III 
IFNs), is a pseudogene in a significant fraction of the human population. A single nucleotide polymorphism located in IFN4, which determines the ability to express 
IFN4-A, has been correlated with poor spontaneous and treatment-induced clearance of hepatitis C virus (HCV) infections.

We show that IFN-4A is an active type III IFN that induces a typical subset of ISGs, 
which are activated by HCV and correlated with antiviral activity of IFN-4A. However, its secretion is impared and this impairment is caused by a yet unknown molecular determinant, but appears to be partially caused by 
weak signal peptide and inefficient N-linked glycosylation. This glycosylation is not 
required for antiviral activity and secretion of IFN-4A, but seems to improve its pro-
cessing. The impaired secretion of IFN-4A appears to be a recently acquired feature 
of primates. 

A single amino acid substitution in IFN-4A changing a proline at position 70 to a 
serine (P70S) alters its activity. We demonstrate that the IFN-4-A/P70 variant has a signif-
ificantly lower antiviral activity compared to IFN-4-A/P70. Our subsequent genetic 
study on a cohort of patients infected with HCV shows that individuals, who encode 
IFN-4-A/P70, display lower hepatic ISG expression, better treatment response rates and better spontaneous clearance rates than patients encoding IFN-4-A/P70. This study 
provides important evidence supporting a role for active IFN-4A as the driver of high 
hepatic ISG expression as well as the cause of poor HCV clearance.

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Pretreatment prediction of individual rheumatoid arthritis patients’ response to 
anti-cytokine therapy using serum cytokine/chemokine/soluble receptor biomarkers

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The inability to match rheumatoid arthritis (RA) patients with the anti-cytokine 
agent most efficacious for them is a major hindrance to patients’ speedy recovery and 
to the clinical use of anti-cytokine therapy. Identifying predictive biomarkers that 
can assist in matching RA patients with more suitable anti-cytokine treatment was 
our aim in this research. The sample consisted of 138 RA patients (naive and 
non-naive) who were administered tocilizumab or etanercept for a minimum of 16 weeks as a prescribed RA treatment. Pretreatment serum samples were obtained from 
patients and clinical measures of their disease activity were evaluated at baseline 
and 16 weeks after treatment commenced. Using patients’ pretreatment serum, we 
measured 31 cytokines/chemokines/soluble receptors and used multiple linear 
regression analysis to identify biomarkers that correlated with patients’ symptom 
levels (DAS28-CRP score) at week 16 and multiple logistic analyses for biomarkers 
that correlated with patients’ final outcome. The results revealed that sgp130, 
logIL-6, logIL-8, logEotaxin, logIL-10, logVEGF, logTNFR-1 and logTNFR-II pretreat-
ment serum levels were predictive of the week 16 DAS28-CRP score in naive tocilizu-
umab patients while sgp130, logGM-CSF and logP-10 were predictive in non-naive 
patients. Additionally, we found logIL-2, logVEGF and logTNFR-II to be less reliable at 
predicting the week 16 DAS28-CRP score in naive etanercept patients. The biomarkers 
for these two therapies differ suggesting that their efficacy will vary for individual 
patients. Biomarkers for tocilizumab, especially sgp130, are involved in RA pathogen-
esis and IL-6 signal transduction, which further suggests that they are highly reliable.

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Innate immune sensing of nucleic acids in airway epithelial cells compared to monocyteic cells

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In the last decade mechanisms for innate immune sensing of pathogen and self 
nucleic acids have been defined. For cytosolic sensing of DNA, the adaptor protein 
STING has a central role, operating downstream of DNA sensors such as cGAS and 
IFI16 to mediate transcription factor activation and cytokine and interferon induction. 
However most of the work in defining cytosolic DNA sensing pathways has been done 
in monocyteic cells, while sensing mechanisms in other frontline sensing cells such as 
airway epithelial cells have been less well defined. Thus here we analysed the innate 
immune response of human airway epithelial cell line models to RNA and DNA, in com-
parison to a human monocytic cell line. Our results show that in both monocyteic and 
epithelial cells the innate immune response to RNA viruses and dsDNA was promptly 
activated. However compared to monocyteic cells, AS49 and BEAS-2B epithelial cells 
failed to produce inflammatory cytokines and interferons in response to DNA viruses 
and dsDNA. These cells lacked expression of IFI16 or STING, but did express cGAS. 
Ectopic expression of STING restored the DNA response in AS49 cells, in a cGAS-depen-
dent manner. In contrast to AS49 and BEAS-2B cells, the epithelial cell line models 
expressed STING and were able to respond to DNA viruses and DNA in a STING-dependent manner. These results highlight the loss of DNA responses in epithelial cell lines lacking STING, and have relevance in consider-
ing different cell models for innate sensing studies in airway epithelial cells.

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Opposing roles of two dsRNA binding proteins PACT and TRBP on RIG-I induced interferon production

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An integral aspect of innate immunity is the ability to detect non-self molecules 
to initiate antiviral signaling via pattern recognition receptors (PRRs). One such