that *miR-1* will have cardiovascular targets far beyond ion channels and transporters.

There are two key therapeutic goals for treating patients with structural heart disease. One is to relieve suffering by improving cardiac performance. The second is to reduce sudden death caused by arrhythmias. Currently, beta 'blockers'[4], drugs that block the action of angiotensin II (ref. 5), and aldosterone antagonists[6] are the only clinically available drug classes that improve heart failure symptoms and reduce sudden death.

More recently, a new target has been identified: inhibition of the multifunctional calcium- and calmodulin-dependent protein kinase II (CaMKII) improves myocardial function and reverses proarrhythmic electrical remodeling after myocardial infarction in mice[7].

Both CaMKII and *miR-1* intersect at the transcription factor myocyte enhancer factor 2 (MEF2) pathway, suggesting that MEF2 signaling might be a common mechanism for controlling hypertrophic and electrical remodeling gene programs. MEF2-activating signals, such as CaMKII, cause cardiac hypertrophy and electrical remodeling. What's more, MEF2 binds an enhancer site for *miR-1* (ref. 8), and MEF2 binding is required for normal expression of the *Drosophila miR-1* homolog *dmiR-1* and normal development of striated muscle in flies[9]. However, it is unknown whether augmenting MEF2 activity increases *miR-1* or whether such an increase would contribute to hypertrophy.

The study by Yang *et al.*[3] makes a strong case that *miR-1* is important for electrical remodeling and arrhythmias, but whether *miR-1* has a role in signaling cardiac hypertrophy is far from certain. Recent studies have shown that *miR-1* is either apparently unchanged[10] or downregulated[11] in cardiac hypertrophy induced by surgical constriction (banding) of the aorta, a well-established model of cardiac hypertrophy. We are in the early stages of understanding how microRNAs modulate cardiovascular disease, and further studies will be necessary before one can assess whether *miR-1* can coordinately signal both electrical remodeling and hypertrophy in surviving myocardium after infarction, or in any other type of structural heart disease.

We now know that *miR-1* is a factor for electrical remodeling after myocardial infarction. This tantalizing new knowledge allows the cardiovascular community to dream—like cancer biologists, immunologists and neuroscientists—of microRNAs as therapeutic targets. Before these musings can become reality, we need to know a lot more.

What cardiovascular disease conditions increase *miR-1*? For example, what is different about surviving myocardial tissue after infarction and hypertrophy? What stress signaling pathways increase and decrease *miR-1*? How do the mouse models, in which stress conditions can be more carefully controlled, mirror or diverge from humans with structural heart disease, in whom multiple conditions—such as coronary artery disease, myocardial infarction, atrial fibrillation and hypertension—often contribute to pathological cellular signaling pathways? Does reducing *miR-1* activity reduce hypertrophy, improve mechanical function and prolong life after myocardial infarction, or any other form of structural heart disease? How long do antisense oligonucleotides work in the heart and can they be modified to target specific receptors[12], rather than delivered by impractical intramyocardial injections?

The work of Yang *et al.*[3] is an exciting step in the dissection of new molecular signaling pathways for arrhythmias and sudden death. At present, there is insufficient information to judge if the new findings are the early rumblings of a therapeutic revolution or a mere tremor.

COMPETING INTERESTS STATEMENT
The authors declare no competing financial interests.

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T effectors outfox T regulators in autoimmunity

Thomas Prod'homme, Martin S Weber & Scott S Zamvil

Findings from a mouse model of multiple sclerosis suggest that regulatory T cells alone cannot outduel pathogenic T cells in the central nervous system. The observations may have implications for experimental approaches designed to dampen autoimmune diseases by infusion of regulatory T cells (pages 423–431).

$CD4^+CD25^+$ regulatory T cells (T-reg) exhibit potent regulatory functions *in vitro* and *in vivo*. These cells play a central role in maintaining peripheral tolerance and controlling organ-specific autoimmunity by suppressing pathogenic autoreactive T cells[1,2]. Defects in T-reg function have been described in several autoimmune diseases, including type I diabetes, rheumatoid arthritis, systemic lupus erythematosus and multiple sclerosis[3]. Strategies that augment T-reg activity are therefore being considered for treatment of these diseases.

In this issue, Korn *et al.*[4] question whether this approach alone is sufficient to control pathogenic T cells in the target organ. They provide evidence that, while migrating and accumulating in the CNS, T-reg are unable to dampen the function of pathogenic effector T cells (T-eff) during the acute phase of experimental autoimmune encephalomyelitis (EAE), a mouse model of multiple sclerosis.

T-reg that develop in the thymus ('natural T-reg') express the transcription factor X-linked forkhead box protein 3 (Foxp3)[5]. T-reg can also be induced *de novo* following exposure to antigen ("adaptive T-reg"). While originally described as anergic owing to their lack of proliferation *in vitro*, it is now established that T-reg proliferate *in vivo* in response to antigen stimulation[6].

It is uncertain whether T-reg exert their suppressive activity primarily in peripheral

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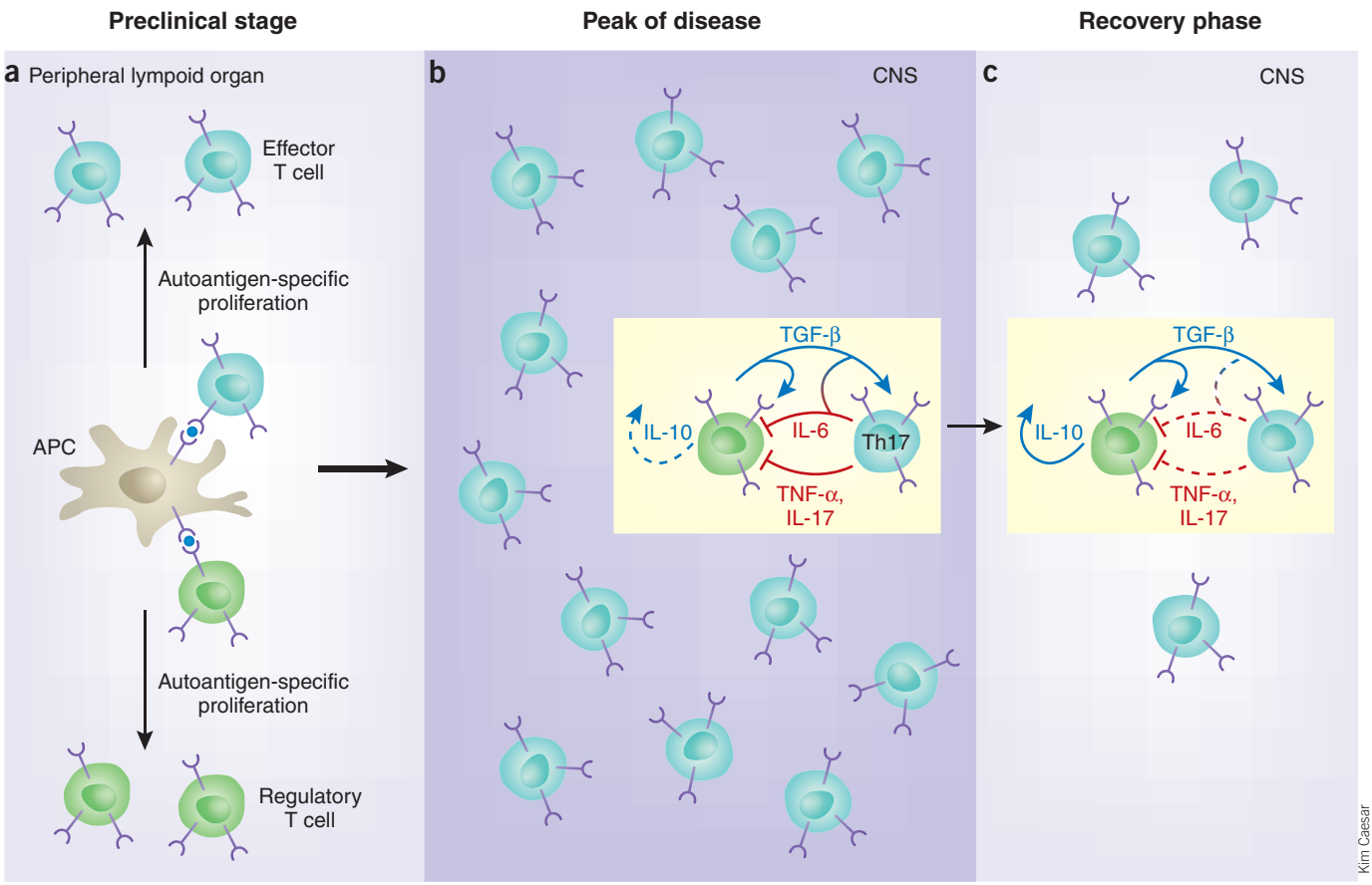

Figure 1 T-reg fail to control CNS T-eff at the peak of EAE. (**a**) Both T-reg and T-eff undergo antigen-specific proliferation in the peripheral lymphoid organs, before their migration into the CNS. (**b**) There, T-eff outnumber T-reg at the peak of the EAE (T-eff:T-reg ratio = 13:1). IL-6, TNF-α and IL-17 production by activated T-eff inhibit T-reg function. In addition, TGF-β production by T-reg, in combination with IL-6, may promote T_H17 differentiation of T-eff. (**c**) However, during recovery, the number of T-eff is reduced while T-reg remain constant (T-eff:T-reg ratio = 4:1), resulting in increased levels of IL-10, a cytokine associated with recovery, and lower secretion of pro-inflammatory cytokines.

lymphoid tissues, or if they must first migrate to their target organ. Various studies with T-cell receptor (TcR)-transgenic mice, in which the T-cell repertoire is restricted, suggest that antigen specificity is important for the activation of T-reg. However, whether antigen specificity is also required for the activity of T-reg arising *in vivo*, in which responses are polyclonal, is less clear.

EAE can be induced via immunization with neural antigens, including myelin oligodendrocyte glycoprotein (MOG). Whether MOG-specific T-reg are expanded *in vivo* and whether they migrate to the CNS during EAE had not been previously investigated. To address these issues, Korn *et al.*[4] took an approach combining mice expressing the T-reg reporter gene *Foxp3gfp* with tetramers of the MOG peptide p35–55/IA^b ($MOG_{35–55}/IA^b$). This approach permitted the authors to track $MOG_{35–55}/IA^b$-specific T-reg *in vivo* during the course of EAE. With these new reagents, they could address the question: which has the upper hand, T-eff or T-reg?

The authors detected MOG-specific $Foxp3^+$ T-reg in both peripheral lymphoid organs and the CNS during EAE. Immunization with $MOG_{35–55}$ did not promote conversion of $Foxp3^-CD4^+$ cells into $Foxp3^+CD4^+$ T cells, arguing in favor of an expansion of pre-existing naturally occurring T-reg. However, this expansion was not restricted to T-reg. Indeed, the authors observed the proliferation of both $MOG_{35–55}/IA^b$-specific T-eff and T-reg in the periphery, before their migration into the CNS.

It seems that T-eff win out during acute EAE: $MOG_{35–55}/IA^b$ T-eff outnumbered T-reg and reached their maximum concentration at the peak of EAE (**Fig. 1**). While CNS $MOG_{35–55}/IA^b$-specific T-reg increased during the preclinical phase, their numbers remained stable during clinical EAE. In recovery, the T-reg:T-eff ratio increased markedly because of the decline in the numbers of T-eff.

Nevertheless, the battle between T-reg and T-eff may not be just a numbers game. The authors found that CNS T-reg suppressed naive and recently activated T-eff isolated from the periphery, but failed to suppress T-eff isolated from the inflamed CNS, even at a 1:1 ratio of T-eff:T-reg.

What accounted for the superiority of T-eff activity in the inflamed CNS? In acute EAE, the inflammatory milieu is conducive to the generation of potent T-eff. The secretion of high levels of interleukin (IL)-6 and tumor necrosis factor (TNF)-α, proinflammatory cytokines, by CNS T-eff was associated with their resistance to suppression.

Recent work has shown that the concomitant secretion of transforming growth factor (TGF)-β and IL-6 leads to the development of pathogenic IL-17–secreting cells (called T-helper type 17, or T_H17), which have a critical role in mediating CNS injury. On the other hand, TGF-β alone promotes the differentiation of T-reg (ref. 7 and **Fig. 1**). As TGF-β is involved in the differentiation of both T-reg and T_H17 cells, it is plausible that secretion of TGF-β by T-reg has a paradoxical effect during acute CNS inflammation, which could act in concert with IL-6 to promote T_H17 differentiation, and inhibit T-reg development[8]. In the recovery phase of EAE, IL-6 is reduced, per-

mitting TGF-β to support T-reg expansion.

Other factors besides natural T-reg may also drive EAE recovery. Korn *et al.*[4] observed elevated CNS production of IL-10, an anti-inflammatory cytokine that has been associated with EAE recovery[9,10]. Increased IL-10 production in recovery corresponded with an expansion of nonspecific (tetramer-negative) CNS T-reg, in sync with the possibility that antigen specificity may not be required for resolution. Interestingly, IL-10 secretion was detected not only within the natural T-reg population, but also within the Foxp3-negative population, suggesting that EAE resolution may result from a collaboration between different regulatory populations—such as the T regulatory type 1 (Tr1) subpopulation of Foxp3$^-$ T-reg, characterized by their secretion of IL-10. Furthermore, the observation that STAT6-deficient mice, which cannot generate the T_H2 subset of anti-inflammatory T cells, develop more severe chronic EAE suggests that T_H2 cells might also contribute to EAE recovery[11].

A major finding by Korn *et al.*[4] is that CNS T-reg do not exhibit any intrinsic defect; rather, CNS T-eff were too potent. Does this mean that a therapy that expands antigen-specific T-reg will be unsuccessful? Not necessarily. While T-reg that developed in EAE pathogenesis could not control CNS T-eff, adoptive transfer of antigen-specific T-reg has been effective in the treatment of EAE as well as in models of rheumatoid arthritis, colitis and type I diabetes. T-reg efficacy may thus be influenced by both the strength of the autoimmune response and the microenvironment in the target tissue[12].

Whether these findings in EAE can be generalized to other organ-specific autoimmune diseases is yet to be determined. But applying the approach developed by Korn *et al.*[4]—using tetramers designed to track T cells for specific autoantigens—should help to further define the interactions between T-reg and their environment in other organ-specific autoimmune diseases.

COMPETING INTERESTS STATEMENT
The authors declare no competing financial interests.

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Premature poking: impulsivity, cocaine and dopamine

George Uhl

'Impulsivity' occurs frequently in people with addiction and other common disorders such as attention deficit hyperactivity disorder (ADHD). Experiments in rats suggest that reduced dopamine receptor availability in the brain's ventral striatum may underlie links between impulsivity and addiction.

Dalley *et al.*[1] have devised an experimental system that connects 'impulsivity', dopamine and addiction in rats. The approach, described in a recent issue of *Science*, suggests that rats chosen for impulsivity also self-administer large amounts of cocaine. The rats also have fewer available D2 class dopamine receptors in the ventral striatum, a site for circuits that underlie reward, movement and responses to novelty.

The findings provide one of the first animal models that clearly links impulsive behaviors, dopamine and stimulant self-administration. The authors validate this approach as a model for the impulsivity found in addicts; if their model proves useful for modeling the impulsivity found in other common human disorders, the advance will prove even more significant.

In humans, several lines of evidence link disorders characterized by impulsivity, dopaminergic brain systems and addictions. High rates of substance dependence occur in individuals who display antisocial personality disorder (ASP) and attention deficit hyperactivity disorder (ADHD)[2,3]. Novelty seeking, 'neuroticism' and pathological gambling are identified more frequently in substance-dependent individuals[3].

Dalley *et al.*[1] have focused on ventral striatal dopamine signaling, since extensive data tie dopamine in this brain area to addiction. Acute administration of virtually every abused substance elevates dopamine release from the striatum. PET studies in addicts have identified different levels of available dopamine D2 class receptors in this region[4]. Genetic associations between variants at the dopamine D2 class receptor (DRD2) dopamine receptor locus and dependence on illegal addictive substances[5] and nicotine have been reproduced repeatedly, even in recent reports by initial skeptics[6,7].

Many brain circuits and neurotransmitter systems are linked to various aspects of addiction. Dopamine circuits provide core contributions to the euphoric properties through which many addictive substances initiate and sustain addictions. They are thus also candidates to contribute to the impulsivity that is often found in addicts.

Taken together, addictions and other disorders with impulsivity at their core are significant societal burdens that justify substantial efforts to improve understanding, prevention and treatment. But it may be difficult to develop a single model for impulsivity traits that encompasses the range of ways in which researchers who study different afflictions—such as addiction, ASP, ADHD, pathological gambling, novelty seeking and prefrontal cortical lesions—view impulsivity. Robbins and colleagues[9] have acknowledged this heterogeneity while at the same time defining impulsivity in more cognitive terms as "action without foresight": "encompass(ing) a range of actions which are poorly conceived, prematurely expressed, unduly risky or inappropriate to the situation and that often result in undesirable consequences".

How Dalley *et al.*[1] assess impulsivity is thus key to interpreting their results. They took advantage of the fact that rats like to explore

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