50 Years Ago

The creation of lawrencium, the eleventh new man-made element beyond uranium (element 92), was announced on April 13 by the University of California and the U.S. Atomic Energy Commission. An isotope of this element was formed on February 14 by bombarding … californium (element 98) with boron-10 or boron-11 nuclei in a heavy-ion linear accelerator at the Lawrence Radiation Laboratory of the University of California; the four nuclear scientists who carried out this experiment … propose to name the new element lawrencium in honour of the late Ernest Orlando Lawrence, inventor of the cyclotron and founder of the laboratory which bears his name … Although it may be possible to create one or two more new elements by this technique, it is improbable that elements beyond number 105 will be synthesized and satisfactorily identified.

From *Nature* 29 April 1961

100 Years Ago

Last summer a pair of robins built their nest in an old fish-basket that was hanging in a shed at the back of my house. All went well until the young birds were about a week old — then happened what appeared to me to be a catastrophe. My Aberdeen terrier pup "Bebe", who must have had some natural desire to catch the mother bird, managed one morning to make a meal of her. Contrary to what I should have expected, the male bird kept close to his young family. Day by day I turned over part of the garden to supply him with a little help in his task. In due course he taught the whole of his young family to fly. I have made enquiries, but cannot find anyone who has had a similar experience, and wondered what your readers might know about such cases.

From *Nature* 27 April 1911

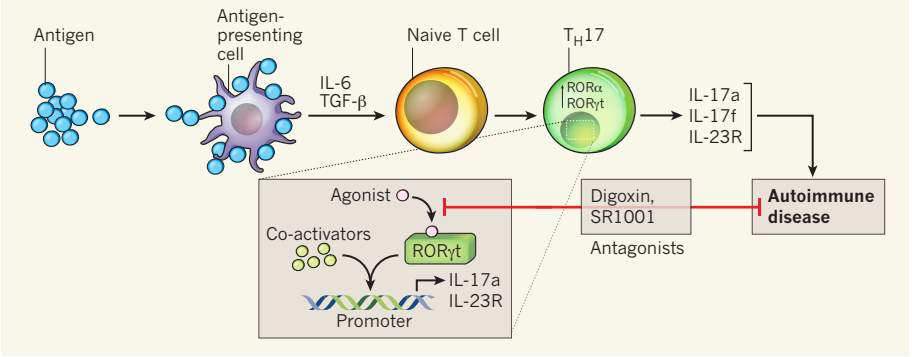

Figure 1 | Effects of digoxin and SR1001 on T_H17 cells. On encountering an antigen on the surface of antigen-presenting cells (and in the presence of IL-6 and TGF-β), naive T cells differentiate into T_H17 cells. This event is associated with expression of the nuclear receptors RORγt and RORα. These receptors, particularly RORγt, are required for T_H17-cell differentiation and for the expression of IL-23R and IL-17a, among other cytokines. Two studies[1,2] show that digoxin and SR1001 bind RORγt, possibly by competing with the natural agonists of these receptors. By inhibiting the recruitment of co-activators and promoting the recruitment of co-repressors, these antagonists reduce RORγt transcriptional activity, T_H17-cell differentiation and IL-17 production, and delay the onset and reduce the severity of autoimmune disease in mice.

of genes encoding IL-17 and the IL-23 receptor (IL23R). The digoxin-induced changes in gene-expression profiles are similar to those observed in RORγ-deficient cells[1], a finding consistent with the notion that digoxin exerts its effects by inhibiting RORγt activity. Previous studies[3,5] demonstrated that expression of either RORα or RORγ in T cells induces the expression of IL-17a. Huh *et al.* show that digoxin inhibits RORγ-dependent, but not RORα-dependent, induction of IL-17a. This result is consistent with the RORγ specificity of digoxin.

Treatment with digoxin or SR1001 greatly inhibited the expression of messenger RNAs for IL23R, IL-17a, IL-17f and IL-22, and markedly reduced production of the IL-17a protein[1,2]. RORγt regulates IL-17a and IL23R expression directly by binding to promoter sequences of the genes encoding these proteins[1,5] (Fig. 1). Treatment with digoxin or SR1001 significantly reduced the binding of RORγt to these sequences. These observations are consistent with the idea that the antagonists' binding causes a conformational change in the ligand-binding domain of the receptors that negatively influences their interaction with co-activators and promotes co-repressor recruitment.

SR1001 showed no obvious toxicity at the doses tested. Digoxin, however, was toxic for human cells at concentrations lower than those needed to inhibit RORγt. Huh *et al.*[1] therefore synthesized digoxin derivatives that retained the RORγt-antagonistic effects but were much less toxic in human cells. Intriguingly, in addition to inhibiting T_H17-cell differentiation, these derivatives increased the expression of IFN-γ and FOXP3 in human $CD4^+$ T cells; these are markers of two other T-cell types, T_H1 and T_{reg} cells, respectively. This finding suggests that inhibiting RORγt activity also promotes the differentiation of human naive T cells into other effector-cell lineages. By contrast, neither digoxin nor SR1001 affected the differentiation of mouse naive T cells into other lineages[1,2].

In mice, loss of RORγ greatly reduces the development of experimental autoimmune encephalomyelitis[3,5]. Both teams[1,2] demonstrated that treatment with either digoxin or SR1001 delays the onset of this disorder in mice and reduces its severity. This was associated with a reduction in the number of T_H17 cells entering the animals' spinal cord. The investigators therefore propose that RORγt antagonists might be effective for treating autoimmune diseases. But first a number of caveats must be considered.

Apart from its expression in T_H17 cells, RORγ is expressed in several other cell types and tissues, in which its function is unknown. It is therefore unclear what side effects long-term treatment might induce in these tissues. Moreover, as recently outlined[7], the role of T_H17 cells and their associated cytokines is complex. So, although inhibiting RORγt may have therapeutic merit for autoimmune disease, it might adversely affect the beneficial functions of these cells in fighting pathogens. Despite these concerns, however, generating more-potent and more-selective derivatives of digoxin and SR1001 could offer attractive strategies for treating autoimmune disorders. ■

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