TNF defined as a therapeutic target for rheumatoid arthritis and other autoimmune diseases

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From immune regulation, through soluble mediators, to autoimmunity (Marc Feldmann)

As a medical student in the late 1960s in Australia, I realized that we knew very little about the mechanisms of disease, and I was eager to learn more. In Melbourne, the premier research institute was the Walter & Eliza Hall Institute (WEHI) of Medical Research, led by the dynamic Gustav Nossal. I began my PhD studies developing the then novel method of immune cell culture, under the supervision of Erwin Diener and Gus Nossal. I used this new approach to investigate mechanisms of immune regulation, with a particular interest in the soluble mediators of immunity, which were subsequently characterized and cloned as cytokines. This interest grew during my post-doctoral research at the Imperial Cancer Research Fund Immunology Unit. At the time no immune responses had been detected to human cancers, so I thought that an approach to generate them might be learned by studying the pathogenesis of human autoimmune diseases, an interest I had acquired at WEHI. In these diseases, immune responses to self tissues do occur, paradoxically, despite the protective role of the immune system. I started by analyzing thyroid diseases, and from this study in the early 1980s I realized that cytokines were likely to be of major importance in their pathogenesis. To study autoimmune tissue and its molecular mediators at the height of the disease was not possible for thyroiditis, but was possible for rheumatoid arthritis, which can be sampled at the height of the disease. I therefore arranged to meet Ravinder Maini, and a fruitful collaboration ensued (**Fig. 1**).

From clinical medicine to clinical science (Ravinder Maini)

During my formative years of training in internal medicine in the late 1960s, the impact of the rheumatic diseases came from the clinic. The ravages of multiple organ involvement in systemic lupus erythematosus and the chronic pain and disability of rheumatoid arthritis were all-too-familiar occurrences. The prospect of insight into disease mechanisms had come from the detection of autoantibodies in blood, and the analysis of cellular and molecular components of the immune reaction in diseased tissues from patients. Rheumatoid arthritis was an obvious choice for my research focus, as tissues from patients were readily accessible by aspiration of joint fluids, biopsies of tissues or access to joint tissue removed during surgical treatment. Because delayed-type hypersensitivity reactions had been implicated in the experimental induction of antigen-induced inflammatory arthritis, my initial interest was in developing *in vitro* assays for the detection of soluble factors implicated in lymphocyte-mediated interactions with inflammatory and mesenchymal cells. These factors were poorly characterized in the late 1960s, however, and offered no insight into the immunopathological events in health and disease. Almost 15 years later, a meeting with Marc Feldmann proved to be of seminal importance to our future work on the identification of tumor necrosis factor (TNF)-α as a key regulator of the inflammatory and tissue-destructive pathways in rheumatoid arthritis.

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Figure 1 Top, Marc Feldmann and Ravinder Maini (2000). Bottom, Fionula Brennan (2000), Richard William (1992) and Jim Woody (1994).

Role of cytokines in autoimmune diseases

The immune system is wonderfully complex and amazingly important to health, as its destruction by HIV demonstrates. But it also has the capacity to do considerably damage to the 'self'. Hence, understanding the autoimmune diseases on a molecular level has been a long-term goal of many research groups. Rheumatoid arthritis, one of the most common autoimmune diseases, attacks the joints, leading to considerable long-term disability and shortened lifespan. The hypothesis that cytokines might be important in the autoimmune disease process came from a series of parallel studies from various laboratories in the early 1980s. These studies showed that in autoimmune diseases such as thyroiditis, diabetes and rheumatoid arthritis[1,2], human leukocyte antigen molecules on the cell surface, especially the class II molecules involved in antigen presentation, are upregulated even on cells such as those of the thyroid epithelium, which do not normally express such molecules. These studies led Feldmann, who had been extensively involved in studies of intercellular signaling molecules, to speculate that the molecules that can augment major histocompatibility complex class II might be of particular pathogenic importance in autoimmunity[3]. At the time, only cytokines such as interferon were known to regulate major histocompatibility complex expression. The opportunity to investigate this hypothesis encouraged Feldmann to change his interest from basic and thyroid autoimmunity to studying cytokine expression in a disease where the tissue can be accessed at the height of disease activity, namely, the synovium in rheumatoid arthritis. This is not possible in thyroditis. The enticing possibility of converting ideas to possible therapeutic targets prompted Feldmann to make the potentially risky move from the well-funded Imperial Cancer Research Fund laboratories to the newly set-up Research Centre at Charing Cross Hospital, in close proximity to Maini's rheumatology clinic and his laboratories at the Kennedy Institute of Rheumatology.

This project of assessing cytokine expression in small pieces of human disease tissue had been made possible by the cloning of cDNAs of cytokines, starting in the early 1980s with the groups of Taniguchi (interferon-β and interleukin (IL)-2)[4], Goeddel (TNF-α and lymphotoxin)[5], Kishimoto (IL-6)[6] and others. The cloning provided probes for mRNA analysis, as well as the possibility of making better antibodies for ELISA and immunohistology.

Rationale for TNF-α as a therapeutic target

Early work in Feldmann's laboratory, chiefly done by Glenn Buchan, a postdoctoral fellow from New Zealand, required the miniaturization of assays to work with restricted human samples and revealed that many different pro- and anti-inflammatory cytokines were overexpressed in the rheumatoid synovium[7]. To understand the basis of the extensive cytokine upregulation, studies were initiated to evaluate cytokine gene regulation in synovial cultures. The cultures developed were different from most rheumatoid cultures at the time, in which monolayers of adherent 'synoviocytes' were passaged for several weeks before being investigated. The 'synoviocytes' studied were fibroblast-like cells, and their study in isolation from the majority (90%) of blood-borne cells infiltrating the joint obviously missed the opportunity of investigating the role of cellular interactions. As immunologists, it made no sense to ignore the immune and inflammatory cells, so Feldmann's laboratory studied the total cell mixture, reflecting the complex interactions of all the cells present *in vivo* in synovium.

Because of the prevailing view that IL-1 was of major importance in inflammatory arthritis, we decided to study the regulation of IL-1 production in total synovial cell culture and found it to be abnormal, with IL-1 mRNA and protein produced over many days. In contrast, in response to immune stimuli, IL-1 mRNA was transiently produced over several hours[8]. This evidence for chronic production of cytokines certainly provided a step forward in our molecular understanding of the pathogenesis of rheumatoid arthritis, but most importantly this observation provided a system to evaluate why IL-1 mRNA production is prolonged in that disease. Again, the cultures of disaggregated mixed synovial cells were key, and our colleague Fionula Brennan conducted the critical experiments in which various antibodies were used as tools to interfere with IL-1 production. These experiments showed that if TNF-α was blocked using specific antibodies (a generous gift from M. Shepard), IL-1 production ceased[9]. This unexpected result indicated that TNF-α had a special role as a proinflammatory cytokine, as it was important in the regulation of another equally strong proinflammatory cytokine, and led to the concept of TNF-α as 'master regulator'. This led to our oft-quoted, oversimplified scheme of the 'TNF-dependent cytokine cascade' (**Fig. 2**). However, this concept was amplified and gained credibility by further studies that showed that TNF

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blockade in synovial cultures reduced production not only of IL-1, but also other inflammatory cytokines, including granulocyte-macrophage colony-stimulating factor, IL-6 and IL-8 (refs. 7,10).

These studies refuted a conceptual dilemma of the time. It was considered by many that with so many proinflammatory cytokines in the synovium, cytokines were not going to be good therapeutic targets, as it was not going to be of much use to block a single cytokine and, clearly, blocking many cytokines with multiple agents would be impractical. But blockade of TNF-α, which at least in culture seemed to result in inhibition of several other cytokines, was thus a therapeutic possibility. The concept of a TNF-α-dependent cytokine cascade was supported by concurrent work by Tony Cerami's group, which showed that antibodies to TNF administered during infection *in vivo* reduced production of IL-1 and IL-6 (ref. 11).

Conclusive support of the rationale for clinical trials of TNF-α blockade in rheumatoid arthritis patients came from other approaches in Maini's laboratory. First, immunohistology of rapidly frozen rheumatoid biopsies indicated that TNF-α was present and that TNF receptors were upregulated *in vivo*[12], in the absence of potential *in vitro* artifacts. Most importantly, in collagen-induced arthritis, using a genetically susceptible mouse model of rheumatoid arthritis, Richard Williams showed that it was possible to ameliorate inflammation and protect cartilage and bone by injecting sufficiently high quantities of an antibody to mouse TNF[13] (generously donated by R. Schreiber). In parallel, George Kollias showed that transgenic mice overexpressing human TNF-α develop a destructive polyarthritis resembling human rheumatoid arthritis[14]. These studies, taken together, showed that the plethora of proinflammatory cytokines was not haphazardly produced, and that it was logical that TNF-α, which is the most rapidly released cytokine after any stress, should coordinate the inflammatory process in experimental systems. Whether this was also true in human patients was the key question.

Proof of principle

Our conviction of the veracity of our preclinical rationale did not find an easy resonance in the biotechnology or pharmaceutical industries. We had become aware of the development of TNF-neutralizing monoclonal antibodies and soluble TNF receptors as candidate therapeutic agents for short-term intervention in acute disorders, such as septic shock, with a poor prognosis and in which TNF-α was implicated. This was due in large part to Cerami and his colleagues, Beutler and Tracey, and their pioneering work on the role of TNF in sepsis[15]. However, many regarded anti-TNF therapy in chronic inflammation as a high-risk strategy. Given the multiplicity of cytokines with similar proinflammatory actions expressed in rheumatoid arthritis, it was thought that other cytokines would emerge to replace TNF. Concerns about safety, immunogenicity, inconvenience of injections and high costs were considered to be equally insurmountable.

Dr. Jim Woody, an ex-colleague of Feldmann and a personal friend who had recently become chief scientist at Centocor Inc., resolved our dilemma. He assisted us in supporting a clinical trial using Centocor's chimeric (human-mouse) TNF-α-specific monoclonal antibody, known as cA2 (subsequently registered as infliximab or Remicade). We initially agreed to treat 10 and then 20 patients with therapy-resistant rheumatoid arthritis with 20 mg/kg in divided intravenous doses over 2 weeks (a dose chosen by extrapolation from our experiments in mouse collagen-induced arthritis), and permitted by Centocor's studies. At this stage, Feldmann's group had been incorporated into the Arthritis Research Campaign (**arc**)'s Kennedy Institute of Rheumatology, later to become part of Imperial College, London.

In 1992, encouraged by the lack of adverse events and the gratifying clinical responses, Maini's clinic had treated all 20 patients in quick succession. Nearly every patient reported a remarkable and rapid improvement in pain, fatigue and mobility. We were concurrently documenting objective reductions in inflammation by loss of swelling and tenderness of joints[16]. Reassuringly, in an open-label study liable to placebo effects, objective laboratory tests detected rapid and dramatic reductions in inflammatory molecules assessed in the blood, such as C-reactive protein[16].

However, the marked anti-inflammatory effect lasted only 6–12 weeks and was followed by recurrence of disease activity. Consequently, a subset of patients was retreated with up to three further cycles of cA2 infusions, and they showed responses of equal magnitude and similar duration[17].

This early experience showed that retreatment with anti-TNF therapy was feasible and might be more important than proof of principle. We communicated the data at several small meetings, and the news spread in the pharmaceutical industry. The stage was set for Centocor, Celltech and Roche, and later Immunex, to pursue dose-ranging phase 2 clinical trials with their anti-TNF agents. Meanwhile, we took the opportunity afforded by the significant change in disease activity to learn more about rheumatoid arthritis pathogenesis by studying the mechanism of action of infliximab, and by helping Centocor devise a randomized, placebo-controlled trial[18]. This was followed by a study of a combination of infliximab and methotrexate[19] (a drug with anti-inflammatory and immunosuppressive properties, commonly used to treat rheumatoid arthritis), based on the synergy associated with reduced immunogenicity we observed with a combination of xenogeneic monoclonal antibodies to TNF and CD4 in the collagen-induced mouse model[20].

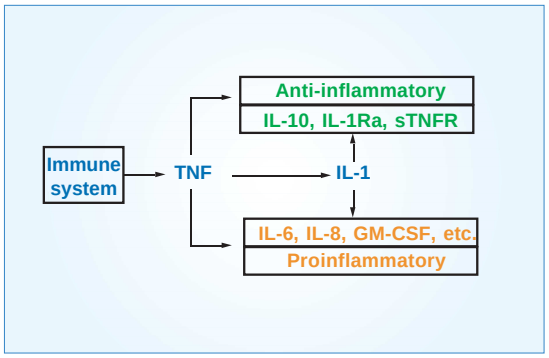

Figure 2 TNF-α-dependent cytokine cascade. TNF has a pivotal role, regulating both pro- and anti-inflammatory mediators. TNF is, in turn, regulated by the immune system. IL-1Ra, IL-1 receptor antagonist; sTNFR, soluble TNF receptor; GM-CSF, granulocyte-macrophage colony-stimulating factor. Reprinted with permission from *Cell* **85**, 307–310; 1996.

Efficacy of anti-TNF therapy

The first randomized, double-blind, placebo-controlled multicenter trial to prove the efficacy of anti-TNF therapy in rheumatoid arthritis was conducted in 1993–1994. In this trial, a single intravenous infusion of infliximab at 1 and 10 mg/kg, or a placebo consisting of 0.1% human serum albumin (to mask the identity of the infusion pack), was administered to therapy-resistant rheumatoid patients. Response rates were 79% and 44% with the high and low doses of

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infliximab, respectively, compared with 8% in the placebo group; these results left no doubt about the efficacy of the treatment[17]. In fact, the responses were so impressive that our nurse was able to accurately predict, before the unblinding of the study, which of the 23 patients from our center had received infliximab or placebo.

The most-feared problem with a chimeric, partly mouse, monoclonal antibody was that infliximab might lose efficacy over time, as a consequence of immunogenicity. This was resolved in the next trial, in which patients with an inadequate response to methotrexate, by then the gold standard of antirheumatoid drugs, were treated with infliximab at 1, 3 or 10 mg/kg, with or without a fixed low dose of methotrexate; the control groups was given placebo infusions and methotrexate[19]. The results showed that the strongest and most durable responses were observed in the groups receiving combination therapy, whereas the placebo group showed no significant response. In this trial, important information about immunogenicity was uncovered: higher doses of infliximab alone, or in combination with methotrexate, proved to be less immunogenic[19]. Future trials of infliximab have therefore used this combination, as has the licensed product used in rheumatoid arthritis.

The combination of other anti-TNF agents and methotrexate has subsequently been shown to be superior to monotherapy in studies with both soluble TNF receptor fusion proteins (etanercept)[21] and a fully human monoclonal antibody (adalimumab)[22]. The combination is currently used in clinical practice for the majority of rheumatoid arthritis patients receiving long-term anti-TNF therapy, and is likely to be of value for long-term treatment of other disorders.

The efficacy of the infliximab-methotrexate combination in a phase 3 trial (ATTRACT) was confirmed, this time in a North American and European multicenter trial headed by Maini and Peter Lipsky, now at the National Institutes of Health. The trials recorded durable control of signs and symptoms in ~50% of the late-stage patients for 2 years. There was a remarkable inhibition, and possible healing, of erosion of bone and loss of cartilage, as assessed by radiographs at 54 and 102 weeks of treatment, exceeding the effects observed with methotrexate alone[23,24]. Most importantly a significant improvement in physical function was sustained over 2 years in patients with moderate to severe impairment at baseline, further supporting the value of anti-TNF therapy even at a late stage of disease[24].

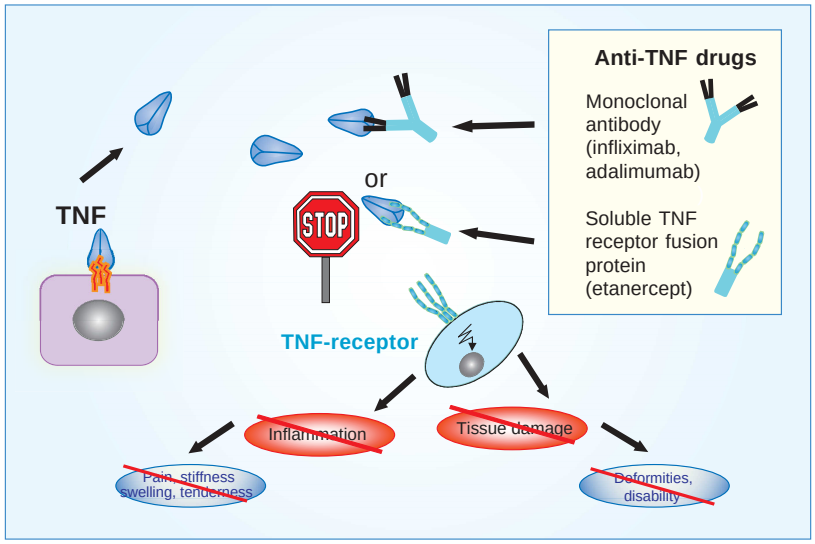

Figure 3 Monoclonal antibodies and TNF receptor fusion protein bind TNF and block its access to TNF receptors on the surface of target cells in joints. This induces inflammation, which leads to symptoms and tissue damage, which leads to deformities.

In clinical trials of other anti-TNF agents, etanercept, a TNF receptor–IgG fusion protein, and adalimumab, a human monoclonal antibody, have similar efficacy profiles, and their availability as self-administered subcutaneous injections increases the choices that patients have as far as routes of administration.

The efficacy proven in clinical trials has now been translated into routine clinical practice. A significant cohort of patients has been under treatment for up to 5 years without loss of efficacy and, in many, a reduction of the dose of corticosteroids or methotrexate previously required to control disease has been possible. It is estimated that over 500,000 patients worldwide have received anti-TNF therapy, the majority for rheumatoid arthritis.

Mechanism of action

The single-shot, randomized, placebo-controlled clinical trial has provided access to serum samples for many studies aimed at understanding the mechanism of action of anti-TNF therapy and unraveling important aspects of the pathogenesis of rheumatoid arthritis. In the first study of the mechanism of action, we showed that C-reactive protein, serum amyloid A protein and haptoglobin were reduced in rheumatoid arthritis, as well as multiple proinflammatory cytokines such as IL-6 and IL-1, verifying the existence of the TNF-dependent cytokine cascade *in vivo*[25]. IL-1 receptor antagonist and soluble TNF receptor concentrations were simultaneously reduced[25]. Concentrations of immunoreactive, but not bioactive TNF-α, were significantly increased from low baseline levels, consistent with the neutralization and trapping of TNF in a TNF-antibody complex. The simultaneous reduction of pro- and anti-inflammatory molecules may explain the lack of restoration of homeostasis in the cytokine network and the relative rarity of sustained remission of disease.

Other studies provided clues and a hypothesis (that there may be altered trafficking) to explain the reduction in cellularity of the synovial membranes that we observed in arthroscopically obtained tissue from knee joints before and after infliximab therapy. Direct evidence of altered cell recruitment was obtained by Peter Taylor, a postdoctoral clinician-scientist working with Maini[26], who found a reduction in the retention of ^{111}In-labeled autologous polymorphs in knee and hand joints after infliximab treatment.

Blockade of TNF-α also results in a reduction in angiogenesis[27] and serum concentrations of matrix metalloproteinases MMP-1 and MMP-3, reflecting their turnover. It seems likely that the arrest of bone damage shown in clinical trials is dependent on the reduction in the recruitment of monocytes and their differentiation into osteoclasts.

Safety

There can be no medical progress without an adequate therapeutic 'window' in which the potential benefits outweigh the potential risks. The role of TNF-α in host defense was

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BOX 1

What do we have yet to learn?

Is there a fundamental difference between the good responders to TNF blockade and the low or nonresponders? If so, is it genetic or is it acquired?

Why are there no cures?

What are the mechanisms of side effects, such as induction of antibody response against double-stranded DNA (frequent), severe infections (less frequent) or possible demyelination (rare)?

What can be safely added to TNF blockade to augment the therapeutic benefit but not the side effects?

Is it possible to block TNF production specifically in the disease tissue?

Why are multiple anticytokine therapies blocking TNF, IL-1, IL-6 or IL-15 effective, whereas anti-immune therapy (against CD4, CD7, CD5 or CD52) is marginal or ineffective?

well established when we embarked on clinical trials, and has been further elaborated since. Hugh McDevitt's laboratory found that TNF-α deficiency may be of etiological importance in a New Zealand mouse model of lupus, and hence there was risk of inducing a lupus-like disease. Both infection and lupus have now been documented in patients given anti-TNF therapy. The numbers are not high, but further risk evaluation and risk-benefit analysis of individual patients is essential, as is careful monitoring during treatment with anti-TNF drugs. As predicted, infusion reactions and injection-site skin reactions also occur, although they rarely precipitate discontinuation of therapy.

The incidence of lymphoma is increased compared with the general population, in clinical trials of infliximab, etanercept and adalimumab, but is in the same range as that reported in rheumatoid patients with severe long-standing disease that have not been exposed to anti-TNF therapies. A review by the US Food and Drug Administration recently concluded that the benefits of TNF blockade exceed the risks based on current information, a view also expressed by multiple editorials (such as ref. 28).

Implications of this work for the future

Despite obvious progress in this field, there are many unanswered questions (see Box 1). The success, both medical and commercial, of the first 'targeted' therapeutic approach in rheumatoid arthritis, TNF blockade, has encouraged many groups to consider trials of anticytokine therapy. In general these have been successful, with IL-1 blockade using the IL-1 receptor antagonist discovered by Arend and Dayer leading to an approved drug (anakinra)[29]. Antibodies to the IL-6 receptor (from Kishimoto's lab)[30] and IL-15 have been successful in early clinical trials. This set of results leads to the concept that proinflammatory cytokines seem, in general, to be good therapeutic targets; in future research it will be important to characterize which, if any, of these has the best efficacy and safety profiles. The safety of IL-1, IL-6 or IL-15 blockade is not yet well defined, as too few patients have been treated in comparison to the >500,000 treated with TNF blockade.

Research into the pathogenesis of the cytokine-dependent autoimmune diseases has been greatly stimulated, with a major goal being to find intracellular targets for orally available drugs that would mimic the efficacy and safety of TNF-α-blocking antibody or receptor. This is not an easy task, and it is not clear when 'pills' will replace the injections of TNF-α blockers.

The anti-TNF clinical studies have shown that antibodies, even those that are not fully human, can be used long-term in patients, and that the immunogenicity issues are real but nevertheless manageable. It seems that the intravenous route favors immunological tolerance, as documented in experimental situations where high zone tolerance to intravenous human gammaglobulin has been extensively studied. Methotrexate coadministration also helps reduce immunogenicity[31].

A key need for effective drugs in rheumatoid arthritis and other autoimmune diseases is tissue protection. In rheumatoid arthritis, dramatic joint protection was noted with three different TNF inhibitors. Joint protection has been a major reason and justification for the significant sales of TNF blockers, despite their substantial costs. But it is puzzling that in many cases, both in rheumatoid arthritis and Crohn disease, there is tissue protection even in the presence of minimal anti-inflammatory effect, as judged clinically. It would thus be very useful to understand in more detail the mechanism by which TNF-α initiates tissue damage.

The success of TNF blockade and its safety has prompted clinical studies of TNF blockade in other diseases, first Crohn disease[32] but then many others, with success reported in juvenile rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis, and approval for these indications by regulatory authorities. Efficacy has been shown in several other diseases, including psoriasis, sarcoidosis, amyloidosis, Behcet syndrome and vasculitis, thus heralding future applications. A key question is why TNF is pivotal in so many chronic inflammatory diseases, as judged by clinical efficacy. A partial answer is that TNF orchestrates the recruitment of leukocytes into joints, upregulating both adhesion molecules and chemokines; this is a crucial step common to all these chronic inflammatory diseases.

Another important consequence of the work we initiated has been the success of antibodies or antibody-like receptor fusion proteins as drugs. This has markedly augmented the interest of the pharmaceutical and biotech industries in antibodies as therapeutics: a considerable fraction of new drugs in clinical trials are now monoclonal antibodies.

How to promote 'bench-to-bedside' developments

There is no doubt that 'translating' scientific concepts into new therapeutics is a hazardous process with many opportunities for failure. Is it possible to distil some of the reasons why we might have succeeded? First, our

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research focused on human pathology and the actual mechanisms of the human disease, not solely on animal models that resemble the human disease. Second, while we developed some of the key methods, questions and concepts, we also used generously donated reagents from a wide spectrum of the international research community, both academic and industrial. Only a small fraction of those are acknowledged here, with the others being acknowledged in our primary papers. Third, we had good links with industry, which enabled us to move forward rapidly once a suitable industrial partner was found. We cannot emphasize enough the importance of personal connections in science of this type.

But perhaps the major point is that no person, no matter how diligent and talented, can be at the forefront of both laboratory and clinical science. We think that, as in our case, the optimum solution may be to have two principal investigators, each with an understanding of the other's overlapping field and a great depth of knowledge in his own. Feldmann, though trained in medicine, has spent his career in various aspects of immunology—immune regulation and the pathogenesis of autoimmune disease. How cells interact has been his special interest, and this evolved into the cytokine studies. Maini specialized in rheumatology but has spent time in the laboratory studying soluble mediators involved in lymphocyte activation, and has focused on the pathology and pathogenesis of disease. Their overlapping interests and skills are apparent. Efficient clinical development of laboratory progress may also depend on intangible, unquantifiable things such as the willingness to collaborate, and to share responsibility and credit. Just as the lone scientist working in isolation is no longer an effective model, it may be that the key to progress in academic clinical science is realizing that optimum skills rest in collaborative groups. The success of our collaboration also depended on our juniors working as an integrated team. But to effectively achieve ambitious goals, it is essential to have an extensive network of scientists, both clinical and basic, who expand the horizons of the possible and are not constrained by 'national' boundaries. The rewards for our group are not only in witnessing an improvement in the human condition, but also in the acquisition of trusted friends.

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CORRIGENDUM: siRNA-directed inhibition of HIV-1 infection

Carl D Novina, Michael F Murray, Derek M Dykxhoorn, Paul J Beresford, Jonathan Riess, Sang-Kyung Lee, Ronald G Collman, Judy Lieberman, Premlata Shankar & Phillip A Sharp
Nat. Med. **8, 681–686 (2002)**

The reported antisense strand of the CD19 siRNA used as a negative control in **Figure 3** (p. 683), with the sequence 5′-GAAUCAUCCUC-CGUCCGGGGU-3′, did not have the appropriate sequence. The CD19 RNA used in **Figure 3** is therefore not relevant as an unrelated siRNA control. Additional experiments using other control siRNAs confirmed that the silencing phenomenon reported in **Figure 3** is specific; the conclusions of the paper remain unchanged. The authors regret the error.

ERRATUM: TNF defined as a therapeutic target for rheumatoid arthritis and other autoimmune diseases

Marc Feldmann & Ravinder N Maini
Nat. Med. **9, 1245–1250 (2003)**

A callout for **Figure 3** should have been inserted on p. 1248. The last sentence of the first paragraph of column 3 should read, "…the relative rarity of sustained remission of disease (**Fig. 3**)." We regret the error.

ERRATUM: β-receptor polymorphisms: heart failure's crystal ball

David A Kass
Nat. Med. **9, 1260–1262 (2003)**

The last sentence of the **Figure 1** legend (p. 1261) is incomplete. The sentence should read, "…contractile depression compared with Gly389 hearts. MHC, myosin heavy chain." We regret the error.

ERRATUM: Confronting ancient scourges (cover image)

Nat. Med. **9 (2003)**

The cover image for the May 2003 issue was not credited. The last sentence of the cover caption should read, "Courtesy of S. Kaufmann and J. Golecki/SPL/Photo Researchers Inc." We regret the error.

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