Objective. To provide an intermediate step between classic arthritis models and clinical trials, the rheumatoid arthritis (RA) synovium SCID mouse model is a valuable tool for use during preclinical research. We undertook this study to investigate the validity of this humanized mouse model using anti–tumor necrosis factor (anti-TNF) and anti–interleukin-1 (anti–IL-1) treatment and to investigate the direct effect of T cells– and B cell–related therapies on the transplanted RA synovial tissue.

Methods. CB17/SCID mice were engrafted with human RA synovial tissue and systemically treated with anti-TNF, anti–IL-1, anti–IL-17, CTLA-4Ig, anti-CD20, or isotype control antibodies.

Results. Validation of the model with anti-TNF treatment significantly reduced serum cytokine levels and decreased histologic inflammation, whereas anti–IL-1 therapy did not show any effect on the RA synovial grafts. In mice engrafted with B cell–rich synovial tissue, anti-CD20 treatment showed clear therapeutic effects. Surprisingly, CTLA-4Ig treatment did not show any effects in this transplantation model, despite pre-screening of the synovial tissue for the presence of CD3+ T cells and the costimulatory molecules CD80 and CD86. In contrast, great therapeutic potential was observed for anti–IL-17 treatment, but only when CD3+ T cells were abundantly present in the RA synovial tissue.

Conclusion. This human RA synovium SCID mouse model enabled us to show that CTLA-4Ig lacks direct effects on T cell activation processes in the synovial tissue. Further evidence was obtained that IL-17 might indeed be an interesting therapeutic target in RA patients with CD3-rich synovial tissue. Further characterization of the RA patients’ individual synovial profiles is of great importance for achieving tailored therapy.

Rheumatoid arthritis (RA) is a systemic autoimmune disease that is characterized by chronic inflammation and destruction of synovial joints. The etiology of RA is still not clear, but its pathogenesis has been studied extensively both in patients and in experimental animal models. During the process of joint inflammation, the synovium is thickened by hyperplasia of the synovial lining as well as by the influx of proinflammatory cells into the joint. Besides the resident synovial fibroblasts and tissue macrophages, immune cells such as neutrophils, natural killer cells, and T and B lympho-
cytes, can be found in the arthritic joint, and all contribute to the final destruction of cartilage and bone matrix.

Animal models of arthritis are widely used to study the potential key players in the process of cartilage (1). Blocking of proinflammatory cytokines or depletion of certain immune cells might improve the outcome of the disease in experimental arthritis models in rats and mice, and thereby help to unravel new therapeutic targets for RA. Unfortunately, not all aspects of animal models can be translated directly to the human situation. The relative roles of tumor necrosis factor α (TNFα) and interleukin-1β (IL-1β) in the pathogenesis of arthritis are a striking example in the field of RA. From in vitro studies and murine arthritis models, IL-1 was found to be a major cytokine in joint pathology, especially driving cartilage destruction, in contrast to the less potent cytokine TNF (2–4). However, clinical trials resulted in the opposite finding: anti-TNF treatment is now the most frequently prescribed biologic agent for RA patients, while blocking IL-1 turned out to have only relatively modest therapeutic effects in this disease (5).

To enhance the predictive value of our research findings in animal models, the use of so-called humanized arthritis models might be a valuable additional tool that can be used during preclinical research. SCID mice are widely used as host for the transplantation of various tissues, since their impaired T and B cell function prevents them from rejecting grafts. Transplantation of human cells or tissue from RA patients into immunodeficient mice enables us to study and target the human homologs of various proteins, such as cytokines, receptors, and growth factors, thereby providing an important step between our standard animal models and clinical trials.

The RA SCID mouse model is used in 2 variants, each with its own advantages and limitations. First described by Geiler et al and Pap et al, cotransplantation of RA synovial tissue or, as more frequently applied, of RA synovial fibroblasts (RASFs) with pieces of cartilage into SCID mice is used to study the capacity of the fibroblast-like synoviocytes to degrade matrix and invade the cartilage (6,7). A recent elegant article reported the migratory and destructive characteristics of RASFs traveling from the transplantation site to healthy cartilage in the contralateral flank (8). Obviously, this cartilage invasion model is limited to one specific cell type as a major key player in the arthritis process, focusing completely on the fibroblast and its destructive mediators and excluding the potential contribution of other cell types to the degradation of cartilage.

The second humanized arthritis model is the RA synovium SCID mouse model. In this model, standardized pieces of synovial tissue from RA patients are transplanted subcutaneously on the back or under the renal capsule of immunodeficient mice (9,10). This model is more complex than the RASF model, since it uses whole RA synovial tissue with a mixture of cell types including various immune cells, preferably freshly isolated during joint surgery. Although this model lacks the possibility of studying destruction of cartilage and/or bone, it is a great model with which to investigate multiple cell types and their interactions within the inflamed synovium, to study the migration of lymphocytes into this tissue (9–11), and to test new therapeutic strategies that target various immunologic aspects of the synovial inflammation. Methotrexate (MTX) treatment in the RA synovium SCID mouse model decreased the inflammatory cells in the graft by inducing apoptosis (12), and previous anti-TNF treatment in the RA synovium SCID mouse model demonstrated a reduced amount of synovial inflammatory cells in these chimeric mice (13). Elegant studies by Klimiuk et al and Takeamura et al in which human T cells and B cells were depleted from the RA synovial grafts showed a crucial role for B cells in T cell activation, whereas T cells drive synovial cytokine and matrix metalloproteinase expression (14,15). Adoptive T cell transfer into the RA synovium SCID mouse model augmented this cytokine production (14).

In our study, we systematically investigated the research value of the RA synovium SCID mouse model using a selection of the most widely prescribed biologic agents that are used in the treatment of RA. First, the validity of this humanized mouse model was studied using anti-TNF and anti–IL-1 treatment. In addition, the direct effect of T cell– and B cell–related therapies on the transplanted RA synovial tissue was investigated with CTLA-4Ig, anti-CD20, and anti–IL-17 antibodies, with specific focus on the responsiveness to anti–IL-17 treatment. In our animal models, we have seen great efficacy of anti–IL-17 treatment, particularly during antigen-specific reactivation of the arthritis and in Th17 cell–driven arthritis models (16,17). Since the presence of T cells seems to be a requirement for successful treatment with IL-17–neutralizing antibodies, we investigated the preselection of synovial tissue to provide tailored treatment for potential anti–IL-17–responsive patients.

**Materials and Methods**

**Mice.** Female CB17/SCID mice were obtained from Charles River. Because of their immune deficiency, all mice
were housed in individually ventilated cages, and a standard diet and water were provided ad libitum. The mice were used between ages 6 and 18 weeks. All animal procedures were approved by the institutional ethics committee.

**Patients and tissues.** Synovial tissue was obtained from 26 RA patients who underwent total joint replacement surgery or synovectomy of the hip, knee, ankle, shoulder, elbow, or wrist joint. The patients were 80.8% female, with a mean age of 64.7 years (range 39–84 years) and a mean disease duration of 18.6 years (range 1–36 years). The RA patients took a variety of antirheumatic drugs: 38.5% were treated with anti-TNF biologic agents (adalimumab, infliximab, etanercept) with or without additional MTX or prednisone, 19.2% were receiving MTX, and the remaining 42.3% took only prednisone, disease-modifying antirheumatic drugs, and/or nonsteroidal antiinflammatory drugs. All patients fulfilled the American College of Rheumatology (ACR) 1987 revised criteria for the classification of RA (18). Procedures were performed after informed consent approved by the hospital ethics committee.

**Study protocol.** Synovial tissue was collected in culture medium with antibiotics and freshly processed into standardized biopsy samples with a diameter of 6 mm using disposable skin biopsy punches (Staffel). Part of the tissue was directly embedded in OCT compound (Tissue-Tek) and snap-frozen in liquid nitrogen, and cryosections were stained with hematoxylin and eosin (H&E) to study the quality and cellularity of the synovial tissue. The rest of the biopsy samples were transplanted to the CB17/SCID mice. CB17/SCID mice, maintained under pathogen-free conditions, were anesthetized by isoflurane inhalation. After swabbing the skin in the neck region with 70% ethanol, a small incision was made in the dorsal skin behind the ear of each SCID mouse, the tissue was inserted subcutaneously, and the wound was closed with suture clips.

**Treatment protocol.** After an engraftment period of 1 week, serum was collected by orbital puncture to screen for the expression of human cytokines and chemokines by Luminex analysis. Mice were randomly assigned to the various treatment groups and treated on days 7 and 10 with intraperitoneal injections of antibodies at a fixed dose of 10 mg/kg. On day 14 after transplantation, the mice were killed by exsanguination, and the grafts were isolated for histologic analysis. For antibody treatment, anti-TNF (adalimumab; Abbott), anti–IL-1 (ACZ885; Novartis), CTLA-4Ig (abatacept; Bristol-Myers Squibb), anti-CD20 (rituximab; Genentech), anti–IL-17 (AIN457; Novartis), or isotype control human IgG1 (Sigma) antibodies were used. All antibodies were specific for their human targets and did not cross-react with the murine homologs.

**Luminex analysis.** To determine levels of the cytokines and chemokines in serum samples, Luminex multianalyte technology in combination with multiplex cytokine kits (Milliplex; Millipore) was used. Cytokines were measured in 25 μl of serum diluted 1:3 in assay buffer. The sensitivity of the multiplex kit was <1 pg/ml. Samples that showed cytokine levels below the detection limit were set at a value of 0.01 pg/ml to include them in further statistical analysis.

**Histologic analysis.** Synovial grafts were isolated on day 14 after transplantation. For standard histology, tissue was embedded in OCT compound, and 6 μm cryosections were subsequently prepared. H&E staining was performed to study synovial inflammation. The severity of inflammation of the graft was scored on an arbitrary scale of 0–2 (0 = no cells, 0.25–0.75 = mild cellularity, 1.0–1.5 = moderate cellularity, and 1.75–2.0 = maximal cellularity).

**Immunohistochemistry.** Cryosections were fixed in 4% paraformaldehyde and incubated with 1% H2O2 in methanol. Next, sections were stained with antibodies against human IL-1β (GF12; Calbiochem), TNFα (AB1793; Abcam), CD3 (MCA1477; Serotec), CD80 (AF140; R&D Systems), CD86 (PN IM2728; Beckman Coulter), and CD20 (CMC302; Cell Marque). Subsequently, the sections were incubated with
biotinylated secondary antibodies (P0260 and P0162; Dako) (BA-5000; Vector) followed by labeling with streptavidin–horseradish peroxidase (P0397; Dako). Peroxidase was developed with diaminobenzidine as substrate. Sections were counterstained with hematoxylin for 1 minute.

**Statistical analysis.** Differences between experimental groups were tested using the Mann-Whitney U test or Kruskal-Wallis test, unless stated otherwise. Results are expressed as the mean ± SEM, unless stated otherwise. *P* values less than 0.05 were considered significant.

**RESULTS**

**Successful validation of the RA synovium SCID mouse model using anti-TNF treatment.** One week after transplantation of synovial tissue into SCID mice, serum was collected and Luminex analysis was performed to screen for human and murine cytokine and chemokine expression in the circulation. Although murine mediators were hardly detected (data not shown), human IL-6 and to a lesser extent human IL-8 and human TNF were clearly present in the serum of the engrafted mice (Figure 1A). Simultaneously with the serum samples, the synovial grafts were collected and scored for histologic cellularity as a measure of inflammation. This analysis demonstrated that serum human IL-6 levels correlated significantly with the histologic inflammation of the synovial grafts (Figure 1B). To validate our model, we used anti-TNF treatment as the most successful biologic agent in the treatment of RA. After an engraftment period of 1 week, mice were injected on days 7 and 10 with adalimumab in an excess amount of 10 mg/kg. On day 14 after transplantation, the mice were killed, and serum and histologic analysis showed a significant reduction of both serum human IL-6 levels and the cellularity of the grafts in mice treated with anti-TNF antibodies compared to the control group (Figures 2A and B). In addition, immunohistochemical staining for human TNFα and IL-1β demonstrated a clear reduction in the synovial expression of these 2 cytokines after anti-TNF treatment (Figures 2C and D).

**Human RA synovial tissue does not respond to anti–IL-1 treatment.** In our classic experimental arthritis models in mice, IL-1 seemed a promising candidate for successful therapeutic targeting in RA. However, IL-1–blocking therapy in clinical trials turned out to be not as effective in RA as expected (5,19). In our humanized mouse model, we tested the effect of anti–IL-1 antibodies in comparison with anti-TNF treatment. In Figure 1A, we had already demonstrated that serum levels of IL-1 in the engrafted SCID mice were much lower than the levels of TNF. Consistent with this finding, the RA synovium SCID mice treated with anti–IL-1 antibodies did not show a significant reduction in serum cytokines and histologic cellularity, whereas the mice engrafted with synovium from the same RA donors did respond significantly to anti-TNF treatment (Figures 3A and B). This result suggests that our humanized mouse model of arthritis reflects the modest responsiveness of RA pa-

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**Figure 2.** A and B, Anti-TNF treatment significantly suppresses serum human IL-6 levels (horizontal lines represent the mean; *** = *P* < 0.001, by Mann-Whitney U test) (A) and histologic scores for cellularity of the synovial grafts in the chimeric mice (B), determined by Luminex analysis 14 days after transplantation (A; 75–77 mice/group) and on hematoxylin and eosin–stained cryosections (B; 36–39 grafts/group). C and D, Anti-TNF treatment also significantly reduces synovial staining with IL-1β (C) and TNFα (D) by immunohistochemistry. Values in B–D are the mean ± SEM. * = *P* < 0.05 versus isotype control treatment, by Mann-Whitney U test. See Figure 1 for definitions.
patients to IL-1 blocking therapy, while neutralizing TNF serves as a positive reference control.

**B cell depletion using anti-CD20 antibodies is effective in the RA synovium SCID mouse model.** Selective depletion of CD20+ B cells has shown good results in the treatment of RA. In our model, we investigated whether the transplanted synovial tissue of RA patients can be responsive to such a B cell therapy by treating the mice with anti-CD20 antibodies. Since not all arthritic tissue obtained during surgery contains B cells, the synovial biopsy samples were first screened for CD20+ B cells by immunohistochemistry before the start of treatment (Figure 4A). As shown in Figure 4B, targeting CD20+ B cells in the RA synovium SCID mouse model significantly reduced the serum levels of human IL-6 as a systemic marker of activation of the synovial graft, to the same extent as our positive control treatment with anti-TNF antibodies. This indicates that the B cell–positive arthritic synovium, despite being isolated from the joint and its supporting immune system, remains directly sensitive to the therapeutic efficacy of anti-CD20 treatment.

**CTLA-4Ig treatment lacks direct therapeutic effects on synovial grafts in the RA synovium SCID mouse model.** In contrast to the positive effect of anti-CD20 antibodies in the RA synovium SCID mouse model,
treatment with CTLA-4Ig did not show any effect. Since the therapeutic effect of CTLA-4Ig is based on binding to the CD80 and CD86 proteins on antigen-presenting cells (APCs), thereby preventing costimulation and activation of T cells, the synovial tissue was first screened for the presence of CD3+ T cells and CD80+ and CD86+ APCs (Figures 5A and B). However, despite this selection the synovial grafts did not respond to CTLA-4Ig treatment either with changes in human IL-6 expression in serum or with changes in histologic inflammation (Figures 5C and D), suggesting that CTLA-4Ig might execute most of its effect not locally in the synovial

Figure 5. A and B, Human rheumatoid arthritis (RA) synovium was stained for CD80+ (A) and CD86+ (B) antigen-presenting cells before treatment of RA synovium SCID mice with CTLA-4Ig. Original magnification × 100. C and D, CTLA-4Ig treatment in the human RA synovium SCID mouse model did not suppress human IL-6 serum levels (C) or histologic scores for cellularity of the synovial grafts in the chimeric mice (D), determined by Luminex analysis 14 days after transplantation (C; 13–14 mice/group) and on hematoxylin and eosin-stained cryosections (D; 13 grafts/group). Horizontal lines in C represent the mean. *** = P < 0.001 versus isotype control treatment, by Mann-Whitney U test. Values in D are the mean ± SEM. See Figure 1 for other definitions.

Figure 6. A and B, Human rheumatoid arthritis (RA) synovium was stained for CD3+ T cells to discriminate between RA tissues with low amounts of CD3+ T cells (A) and high amounts of CD3+ T cells (B). Original magnification × 100. C, Anti-interleukin-17 (anti-IL-17) treatment in the human RA synovium SCID mouse model significantly suppressed human IL-6 (hIL-6) levels in the serum of the mice engrafted with CD3-rich synovial tissue, but not with synovial tissue with low amounts of CD3, determined by Luminex analysis 14 days after transplantation (9–11 mice/group). Horizontal lines represent the mean. * = P < 0.05 versus isotype control treatment, by Mann-Whitney U test.
tissue, but mainly systemically in lymphoid structures like spleen and lymph nodes to reach clinical efficacy in RA patients.

**Responsiveness to anti–IL-17 treatment is determined by CD3 + T cells in synovium.** Although CTLA-4Ig, inhibiting the T cell costimulation process, was not effective in our RA synovium SCID mouse model, this does not necessarily mean that the RA synovium SCID mouse model is not sensitive to any T cell–based therapy. Therefore, we investigated the effect of blocking the T cell effector cytokine IL-17 in the RA synovium SCID mice. Before the start of treatment, human RA synovial tissue was stained for the presence of CD3 + T cells, the major source of IL-17 production. As shown in Figures 6A and B, two groups could be clearly distinguished: synovium with low numbers of CD3 + T cells diffusely spread or clustered around small blood vessels (CD3low), and tissue with high amounts of CD3 + T cells, mainly aggregated in large lymphocyte clusters (CD3high). Initially it seemed that despite the presence of CD3+ T cells in the synovial tissue, the engrafted SCID mice did not show a response to anti–IL-17, as demonstrated by levels of human IL-6 in serum comparable to those in control-treated mice (Figure 6C). Interestingly, after stratification for CD3low and CD3high synovial tissue, only the mice transplanted with the synovium rich in CD3 + T cells showed a significant response to anti–IL-17 treatment (Figure 6C), suggesting that the relative presence of CD3 + T cells in the arthritic joint is a good marker for responsiveness to this type of treatment.

The first clinical trials with anti–IL-17 treatment in RA patients showed promising numbers of patients meeting the ACR 20% improvement criteria (20,21). However, in our opinion, preselection of the patients before treatment, based on the presence of CD3 + T cells in the synovial tissue, might further improve clinical responses to blocking IL-17.

**DISCUSSION**

This is the first study in the human RA synovium SCID mouse model that has systematically validated and screened the predictive value of such a humanized arthritis model by testing the therapeutic effectiveness of widely accepted biologic treatments for RA. In addition, based on the findings of this study, we would like to propose a selection method based on CD3+ T cell screening to enhance the therapeutic responsiveness of RA patients to anti–IL-17 treatment.

The RA synovium SCID mouse model seems to be a very suitable tool for screening the therapeutic efficacy of new biologic agents and promising chemical compounds on inflamed RA synovial tissue. In several respects, the RA synovium SCID mouse model is superior to in vitro synovium explant studies. Although the in vivo model requires far more synovial tissue than is needed for in vitro studies, the engraftment of SCID mice results in a dynamic model with good vascularization of the tissue within 1 week after engraftment. In vitro synovial explant cultures, mainly used for stimulation assays, can also be used to study the antinflammatory effect of various inhibitors on the spontaneous secretion of cytokines and chemokines, but readout is often limited to 24–48 hours of culture (22,23). The good vascularity of the synovium in the RA synovium SCID mouse model enables prolonged cell survival up to weeks after engraftment (10,11), and also improves targeting of the tissue with potential new therapeutics.

Initially we performed several RA synovium SCID mouse model experiments to investigate the therapeutic window of this arthritis model using anti-TNF as a widely accepted biologic agent. For this purpose, adalimumab was selected because of its fully humanized structure, which does not cross-react with murine TNFα. Anti-TNF treatment in this model significantly and consistently reduced serum human IL-6 levels, and suppressed inflammation scores of the synovial grafts being analyzed for cellularity as well as proinflammatory cytokine staining by immunohistochemistry. In the set-up phase of the model, various serologic markers were determined in the engrafted SCID mice using Luminex and enzyme-linked immunosorbent assay technique. Human IL-6 was most abundantly present in the serum of the RA synovium SCID mice, but human IL-8 levels, although 10-fold lower, showed a pattern similar to that of human IL-6, correlating with the inflammatory status of the grafts and responding to anti-TNF treatment. Consistent with earlier findings (11), human IgG and, to a lesser extent, human IgM were detected in the serum of our SCID mice engrafted with RA synovial tissue. Because of the various IgG1 antibody treatments in this study, human IgG were not used as a readout in our SCID mouse experiments, but human IgG levels might be a very useful additional readout when testing new chemical entities in this model.

After successful validation of the model with anti-TNF antibodies, the effect of IL-1 blocking was investigated in this RA synovium SCID mouse model. Although a trend toward therapeutic efficacy was observed, no significant suppressive effect of anti–IL-1 treatment was found on both serum IL-6 levels and histologic scores. This result is in line with the clinical
finding that blocking IL-1 in RA patients resulted in quite modest responses (5). Two important remarks must be made concerning the potential underestimation of the effect of anti–IL-1 treatment. First, the followup of the RA synovium SCID mice injected with anti–IL-1 antibodies was restricted to 1 week of treatment, while the first clinical effects of IL-1 blockers in RA patients were only reported after 24 weeks of treatment (24). In addition, during the validation of the RA synovium SCID mouse model with anti-TNF and anti–IL-1 treatment, we deliberately chose not to preselect the RA synovial tissue for the presence of certain target cells or proteins. However, since IL-1 plays a crucial role in T cell activation and Th17 cell differentiation, screening for and selection of CD3-rich synovial tissue might increase the responsiveness to anti–IL-1 treatment. Further RA synovium SCID mouse studies are needed to investigate the potential of such selection criteria, which might result in an interesting change of practice for the treatment of RA patients with IL-1 blockers.

While B cell targeting in the RA synovium SCID mouse model using anti-CD20 antibodies resulted in clear therapeutic effects, the lack of any response to CTLA-4Ig treatment was quite surprising. After engraftment of SCID mice with RA synovial tissue, low levels of human IL-17 and interferon-γ could be detected in the serum of some of the mice (data not shown), indicating the presence of activated Th17 and Th1 cells in the synovial grafts. Despite optimal selection of potentially responsive synovial tissues after immunohistochemistry for various markers involved in APC–T cell interaction, CTLA-4Ig did not reduce serum cytokine levels or histologic scores. Based on these results, we could speculate that abatacept treatment does not act directly on the synovium, but more likely prevents T cell activation at a systemic level of the immune system. More complicated humanized arthritis models integrating RA synovial tissue and human peripheral blood mononuclear cells need to be developed to test this hypothesis.

Although CTLA-4Ig treatment in our RA synovium SCID mouse model failed, neutralizing IL-17 as another target involving T cells did show significant therapeutic effects. Interestingly, the relative presence of CD3+ T cells clearly determined the responsiveness of the engrafted mice to the anti–IL-17 antibodies. Stratification of the RA synovial tissue by expression of high and low amounts of CD3+ T cells resulted both in good responders and in mice that did not respond to anti–IL-17 treatment, respectively. These findings suggest that a selection method based on CD3+ T cell screening might be very useful in daily practice to provide tailored therapy to RA patients, and to enhance the therapeutic responsiveness of these patients to anti–IL-17 treatment. Despite successful validation of the RA synovium SCID mouse model with various biologic treatments, in this study we could not yet link the responsiveness of the synovial grafts to the clinical responses of the patients, except for anti-TNF treatment, because these patients were not treated with biologic agents other than TNF blockers. Future studies in the RA synovium SCID mouse model might provide such a correlation of efficacy for various specific biotherapies.

In conclusion, our studies show that the RA synovium SCID mouse model mirrors most clinical observations with biologic treatments in RA patients. Consequently, the predictive value of this model for evaluating novel treatments is expected to be high. Moreover, the model allows for studies of RA heterogeneity, which can be exploited to optimize protocols for targeted treatment in preselected patient groups.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. van den Berg had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.


Acquisition of data. Koenders, Marijnissen, Abdollahi-Roodsaz, Dulos, Boots.

Analysis and interpretation of data. Koenders, Marijnissen, Joosten, Abdollahi-Roodsaz, van de Loo, Dulos, van den Berg, Boots.

ROLE OF THE STUDY SPONSOR

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ADDITIONAL DISCLOSURE

Author Di Padova is an employee of Novartis Pharma.
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