VIEWPOINT

# The resolution of inflammation

*Christopher D. Buckley, Derek W. Gilroy, Charles N. Serhan, Brigitta Stockinger and Paul P. Tak*

Abstract | In 2012, *Nature Reviews Immunology* organized a conference that brought together scientists and clinicians from both academia and industry to discuss one of the most pressing questions in medicine — how do we turn off rampant, undesirable inflammation? There is a growing appreciation that, similarly to the initiation of inflammation, the resolution of inflammation is an intricate and active process. Can we therefore harness the mediators involved in resolution responses to treat patients with chronic inflammatory or autoimmune diseases? Here, we ask five of the speakers from the conference to share their thoughts on this emerging field.

*Originally, the resolution of inflammation was considered to be a passive process. In your opinion, what are the key observations that demonstrate that resolution is, in fact, an active process, and why is this important?*

**Christopher D. Buckley.** Acute inflammation is an unstable state; it either resolves or persists. Traditional models of inflammation proposed that inflammation resolved following the removal of the pro-inflammatory mediators that initiated the response in the first place — that is, catabolism was sufficient for inflammation to 'burn out'. A return to homeostasis was argued to occur solely by passive means.

However, several anti-inflammatory agents have now been discovered, including steroids, nitric oxide, adenosine and interleukin-10 (IL-10), as well as regulatory T ($T_{Reg}$) cells. These regulators inhibit immune responses and put the brakes on inflammation[1]. Such observations have challenged the idea that the resolution of inflammation is simply a catabolic process.

Another step forward was the molecular characterization of several distinct biochemical pathways that are actively turned on when inflammation is induced and lead to the production of eicosanoids and other lipid mediators that have pro-resolving or reparatory functions[2]. Experiments involving genetic deletion models or the pharmacological synthesis of these pro-resolving compounds provided compelling evidence that they have a key role in regulating inflammatory responses[3]. Indeed, the inflammatory cascade mirrors many other cascades in biology (such as the complement and coagulation pathways) in that 'the beginning programs the end'[4].

**Paul P. Tak.** Why would the resolution of inflammation be an active process? My first argument is teleological in nature. When the exogenous cause of the inflammatory response has been eliminated, a failure to resolve tissue inflammation affects energy metabolism and may result in further tissue damage. If, for instance, neutrophils and eosinophils that migrated to the site of inflammation stayed unchecked after the elimination of the injurious stimulus, they could cause excessive tissue damage. Therefore, active clearance of inflammatory infiltrates by phagocytosis is required. In addition, there is a complex interplay of cellular mechanisms and soluble mediators that are actively turned on during the resolution phase of inflammation[5].

The monocytes and macrophages that are involved in cell clearance may help to prepare the tissue for the resolution of inflammation and tissue repair. Other cell types that have been shown to be intimately involved in resolving inflammation include $T_{Reg}$ cells, parenchymal cells (such as the epithelium) and stromal cells. Mediators that are produced locally during the resolution phase include lipoxins, resolvins, prostaglandins of the D series, anti-inflammatory cytokines, adenosine, microRNAs and inhibitors of pattern-recognition receptors. The deletion of genes encoding inhibitors of Toll-like receptors (TLRs) and NOD-like receptors (NLRs) leads to a state of hyperinflammation, supporting the notion that active control of inflammation is important[6].

In addition to local processes, systemic mechanisms, in particular the release of anti-inflammatory hormones such as cortisol, and the induction of neural mechanisms, such as the cholinergic anti-inflammatory pathway[7], have been demonstrated to have a key role in actively suppressing inflammation.

**Charles N. Serhan.** More than 100 years ago, Metchnikoff found that neutrophils are ingested by tissue macrophages (the 'big eaters') and that this clearance of neutrophils resolves tissue inflammation[8–10]. Subsequent research identified the 'go' signals (for example, complement components, cytokines, chemokines and lipid mediators) that promote the recruitment of leukocytes from the blood to the inflamed tissue. Investigators believed that the removal of the inflammatory stimulus prevented the production of chemoattractants that promote further leukocyte recruitment. As such, they thought that simple dilution of chemoattractants in the tissue prevented further inflammatory cell recruitment and that passive events were involved in ending inflammation.

However, evidence that the resolution of inflammation is, in fact, an active process came from studying acute self-limiting responses and using a systems-based approach[2,4,5,11]. These studies showed that, in resolving inflammatory exudates, cell–cell interactions lead to the generation of active signals that limit further neutrophil recruitment to the tissue and enhance the engulfment of neutrophils by macrophages, thereby promoting a return

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Charles N. Serhan studied biochemistry at Stony Brook University, New York, USA, and gained a doctorate in medical sciences from New York University School of Medicine in 1982. He subsequently trained in physiological chemistry at the Karolinska Institutet, Stockholm, Sweden, with Bengt Samuelsson. In 1987, he joined the faculty at Harvard Medical School, Boston, Massachusetts, USA, and he received an honorary degree in 1996 from Harvard University. Since 1995, he has been Director of the Center for Experimental Therapeutics and Reperfusion Injury at Brigham and Women's Hospital, Boston, Massachusetts, USA; Simon Gelman Professor of Anaesthesia (Biochemistry and Molecular Pharmacology) at Harvard Medical School; and Professor of Oral Medicine, Infection and Immunity. His research focuses on the structural elucidation of novel mediators and their mechanisms of action in the resolution of inflammation and infection.

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to homeostasis. A key step in this active resolution process is the occurrence of lipid-mediator class-switching in exudates. That is, prostaglandins involved in the initiation phase of inflammation activate the translation of mRNAs encoding enzymes that are necessary for the production of 'immunoresolvents' (namely, lipoxins, resolvins and protectins) during the resolution phase[2,4,5,12].

An important point to consider is what distinguishes a pro-resolving mediator from an anti-inflammatory one? I would say that pro-resolving mediators can be defined by their ability to: one, counter-regulate mediators that summon leukocytes to the inflamed site; two, dampen pain; three, stimulate non-phlogistic monocyte recruitment[5,13]; and, four, activate macrophages in a manner that enhances the efferocytosis of apoptotic granulocytes and promotes the clearance of tissue debris[14]. Active resolution also evokes specialized signalling pathways, including nuclear factor-κB (NF-κB)-regulated processes (which can be either stimulatory or inhibitory, depending on the ligand and the cellular process[15]) and ATP metabolism[16]. For example, the activation of the resolvin E1 receptor functions to block and counter tumour necrosis factor (TNF)-induced NF-κB signalling. Together, these resolution-phase mediators and pathways orchestrate a clean-up of the exudate and tissue regeneration.

**Q** *Are there general mechanisms that promote the resolution of inflammation or are the mechanisms involved tissue specific? Do we understand how different types of inflammatory response (for example, $T_H17$-type versus $T_H2$-type) are resolved?*

**C.N.S.** To answer this question, we should consider how the body deals with exudative inflammation. There are three types of exudate: one, a purulent exudate or pus; two, a haemorrhagic, stained and grossly bloody exudate; and three, a serous, protein-rich fluid that resembles serum but lacks fibrinogen and platelets and has only small numbers of infiltrated leukocytes (for example, the fluid in a blister following a mild skin burn)[17]. As these inflammatory exudates are defined by different cellular compositions and contain different local chemical mediators and proteins, a 'one size fits all' approach is unlikely to be sufficient to resolve inflammation in each scenario. In my opinion, it is very likely that specific mechanisms evolved to actively resolve each type of pus or exudate that can affect different tissues or organs.

The key thing to appreciate here is that a better understanding of the mechanisms and mediators that promote the resolution of each type of inflammatory exudate might allow us to identify pro-resolving mediators that could be exploited for therapeutic purposes.

In experimental animal settings, there is substantial evidence for generalized programmed sequential responses during inflammation. For example, tissue oedema is followed by neutrophilic infiltration; then there is an eventual loss of neutrophils from the site and non-phlogistic recruitment of mononuclear cells, which fill the tissue site or cavity to form exudates. This sequential process involves the concomitant local biosynthesis of pro-inflammatory and pro-resolving chemical mediators, and it can be thought of as the 'general' programme involved in the initiation and termination of an acute inflammatory response.

However, the general cellular sequence of events that contribute to the cardinal signs of inflammation (namely, heat, swelling, redness and pain[17]) can change depending on the presence of tissue macrophages, mast cells or even eosinophils within distinct tissues or organs[18]. As such, depending on the tissue that is affected and the type of injury experienced, the first cells to respond to an injury could be tissue-resident macrophages, polymorphonuclear leukocytes (PMNs), platelets, endothelial cells or epithelial cells. The composition of local mediators in the tissue directly reflects the temporal activation of the specific cell types involved in these processes, and it is likely that the resolution response is also shaped in a site-specific manner.

Our field is still investigating how different forms of inflammation (for example, sterile, infectious or allergic inflammation) are ultimately resolved. Along these lines, it has been shown that resolvin E1 down-regulates T helper 17 ($T_H17$)-type inflammatory responses[19], whereas during $T_H2$-type conditions human T cells produce protectin D1 to regulate leukocyte trafficking and

survival[20]. Protectin D1 stops further PMN influx and stimulates the uptake of both microbial products and apoptotic PMNs by macrophages[21]. Protectin D1 also promotes the removal of phagocytes through lymphatics, regulates T cell migration and inhibits caspase- and BAX-mediated signalling to regulate T cell longevity.

**Derek W. Gilroy.** During the resolution of chemical- or bacterium-induced inflammation, separate populations of macrophages have different tasks. Tissue-resident macrophages are responsible for the non-phlogistic clearance of antigen-bearing apoptotic cells and the maintenance of tolerance, whereas monocyte-derived macrophages engulf antigens to generate long-term immune memory. The failure of macrophages to remove apoptotic cells is suggested to break tolerance and predispose to autoimmunity[22]. Concomitantly with macrophage influx during the resolution of these types of inflammation, there is recruitment of innate-like lymphocytes that control the strength of the immune response to secondary infections[23].

By contrast, the resolution of virus-induced respiratory inflammation is characterized by a prolonged period of immune suppression, which is a result of the sustained desensitization of lung sentinel cells to TLR ligands[24]. In experimental liver fibrosis, macrophages promote the accumulation of extracellular matrix during injury development, but they enhance matrix degradation during the resolution phase[25]; this matrix-degrading phenotype is not apparent during the resolution of infectious inflammatory responses[26]. Moreover, TNF-related apoptosis-inducing ligand (TRAIL) is essential for the resolution of granulomatous experimental autoimmune thyroiditis[27].

Therefore, different cells, phenotypes and biochemical pathways are required to resolve distinct inflammatory responses in different tissues. And unless there is a humoral factor, cell or signalling pathway common to these diverse processes, it is likely that pro-resolution processes are tissue and stimulus specific.

Indeed, each phase of the disease may also require a unique set of pro-resolution events. For instance, resolving joint inflammation during the early stages of arthritis onset is arguably less challenging than resolving inflammation in a joint that is characterized by advanced bone destruction and the presence of pannus tissue, lymphangiogenesis and tertiary lymphoid tissues.

**C.D.B.** Inflammatory responses begin where damage occurs (which can be due to physical or chemical injury or infection). Historically, models of inflammation have stressed a major role for antigen-specific lymphocyte responses in defining how the inflammatory response begins and how it is subsequently moulded. However, recent studies have challenged the primacy of the leukocyte and instead have begun to focus on an extended innate immune system in which stromal cells play a part in regulating the persistence of the inflammatory lesion[28]. In the same way that the induction of inflammation has both 'generic' and 'tissue-specific' features, it is very likely that the mechanisms involved in promoting the resolution of inflammation have both 'public' and 'private' characteristics.

There is now accumulating evidence that stromal cells define tissue topography, provide positional memory and regulate the switch from resolving to persistent inflammation[29]. Furthermore, in ankylosing spondylitis, a unique population of innate lymphoid cells located in the enthesis has recently been shown to provide a mechanistic link between systemic changes in IL-23 expression levels and resulting inflammation at this precise anatomical site[30]. Given that all inflammatory reactions take place within a defined background of specialized stromal cells, understanding the biology of these cells will be important in elucidating how immune cell infiltrates become established and whether there are tissue-specific ways in which immune-mediated inflammatory diseases persist or resolve.

**P.P.T.** The question of whether general or tissue-specific mechanisms are involved in the resolution of inflammation should be answered in a dialectic way, as they are both important. For instance, low levels of serum cortisol are associated with higher levels of synovial inflammation in rheumatoid arthritis. Aggravation of arthritis is also observed in nicotinic acetylcholine receptor α7 subunit gene-knockout mice, in which the systemic cholinergic system cannot exert its anti-inflammatory effects[31,32]. Together, these observations show that if general anti-inflammatory mechanisms fail, this results in increased disease activity at the site of inflammation.

Several mechanisms promoting the resolution of inflammation are in principle generic, but become operative in the inflamed microenvironment. Examples are the induction of apoptosis and phagocytosis, the release of anti-inflammatory mediators at the site of inflammation, and tissue infiltration by macrophages and $T_{Reg}$ cells with anti-inflammatory properties or the differentiation of these cell types within the inflamed compartment. The same mechanisms may be activated when tissue injury occurs at other sites. Finally, tissue-specific cells are involved in determining whether inflammation persists or resolves.

Also, as C.D.B. mentions, the stromal milieu is involved in directing leukocyte behaviour in inflamed tissues, and for the resolution of inflammation to occur activated stromal cells need to revert back to their non-inflammatory phenotype[33]. Local inflammation could, however, induce genetic and epigenetic changes in mesenchymal cells, which would block this reversion and result in autonomous disease progression[34].

The roles of different types of inflammatory response may differ between different tissues and may also depend on the cause of tissue injury. The resolution of neuroborreliosis (which arises following infection of the central nervous system by *Borrelia burgdorferi,* the causative agent of Lyme disease) appears to be associated with a strong $T_H1$-type response followed by a $T_H2$-type response. By contrast, a $T_H17$-type response has been associated with ongoing inflammation in Lyme arthritis. The fact that the same infectious agent can cause distinct types of inflammation at different tissue sites suggests that distinct resolution mechanisms will also operate in different tissues. And another point to note is that, although $T_H17$-type inflammation seems to prolong the inflammatory response in Lyme arthritis, IL-17-producing γδ T cells can promote the resolution of allergic airway inflammation[35].

Future work should provide more insight into the roles of specific inflammatory responses in different conditions, during distinct stages of disease, taking into account the plasticity of the response and the differences between mice and humans.

**Brigitta Stockinger.** I would assume that certain mediators of resolution are generally applicable to any type of inflammation, but there must be type-specific mediators too. Different insults to homeostasis demand differentially targeted responses and as a result there may also be distinct mechanisms of resolution.

For instance, inflammation at barrier sites that trigger IL-17-mediated responses — starting with innate γδ T cell-mediated IL-17 production, which is essential for sustaining neutrophil responses — is likely to involve

different control mechanisms from inflammation of the lung as a result of an allergic insult. As the main focus at present is on the changes in innate immune cell types (such as neutrophils and macrophages) during the resolution of inflammation, very little is known about the role of T cells, particularly adaptive T cells.

One current misconception in the field is that the phagocytosis of apoptotic neutrophils always results in a tolerogenic stimulus. This needs to be redefined in view of recent evidence that such a process can, in fact, be highly pro-inflammatory, and lead to the induction of adaptive $T_H17$ cell responses, if the neutrophils were involved in dealing with an infectious agent[36].

The propagation of an adaptive $T_H17$ cell response is potentially dangerous because of the link between these cells and various autoimmune syndromes. However, this is absolutely dependent on the cytokine IL-23, which is released by innate cells such as dendritic cells and macrophages. Although the mediators that antagonize IL-23 are known, it is currently completely unknown how and by what these processes are controlled in a temporal manner during inflammatory processes and their resolution.

Regarding the resolution of allergy- or helminth-inflicted damage, emerging data suggest an important role for innate lymphoid cells and their mediators. However, the interactions of these cells with the innate immune cells that are the current focus of research on the resolution of inflammation remain unclear at present.

**D.W.G.** As well as the pro-resolving and anti-inflammatory mediators already discussed, it is important to remember that for effective resolution to occur the injurious agents that triggered the inflammatory response must be eliminated; without this, inflammation will not resolve. In the case of bacterial infection, for instance, this is facilitated, in part, by NADPH oxidase-mediated killing[37]. Defects in the assembly of NADPH oxidase subunits, as occur in chronic granulomatous disease, exemplify beautifully the prime importance of antigen clearance in resolution biology[38]. Therefore, regardless of how sophisticated a pro-resolution pharmacopoeia may be, inflammation will not abate unless the injurious stimulus is cleared. This becomes important for diseases such as rheumatoid arthritis and systemic lupus erythematosus, for instance, which are supposedly driven by endogenous antigens.

Following stimulus removal, which alleviates the pro-inflammatory state and prevents further activation of pro-inflammatory signalling pathways, the next question is which tissues and mechanisms sense that danger has been eliminated and that inflammation can begin to resolve? Then, once the resolving processes are under way, several steps are necessary for complete resolution. One, leukocyte trafficking must cease. Two, pro-inflammatory mediators must be catabolized. Three, mononuclear phagocytes possessing a pro-resolution phenotype must clear cell debris, in particular apoptotic cells (to prevent autoimmunity). Four, inflammatory monocytes and macrophages must be cleared. And, five, the injured tissue must revert back to its pre-inflamed homeostatic state; in the case of the peritoneal cavity, this involves repopulation by innate and memory lymphocytes[1].

However, I believe that such tissues, while resolving inflammation at the macroscopic level, remain altered in terms of their cell profiles and phenotypes for weeks or even months. Therefore, inasmuch as inflammatory onset is driven by a complex sequence of overlapping factors, resolution is equally intricate and active. Resolution processes may therefore be akin to those that occur following vaccination[39].

## Glossary

**Cholinergic anti-inflammatory pathway**
A mechanism for neural inhibition of local and systemic inflammation that is controlled by vagus nerve stimulation.

**Efferocytosis**
The process by which dead or dying cells are removed through engulfment by phagocytes.

**Eicosanoids**
(Also known as icosanoids). A general term used to denote bioactive lipid mediators that contain 20 carbon atoms and are synthesized from arachidonic acid (a fatty acid present in membrane phospholipids) by the initial activities of either cyclooxygenases or lipoxygenases. Examples include prostaglandins, leukotrienes and lipoxins. Eicosanoids signal through G protein-coupled receptors and have important roles in inflammation, but also in many other biological processes, including reproduction and haemostasis.

**Enthesis**
The region at the junction between tendon and bone. This is a key site of pathology in spondyloarthritic diseases, such as ankylosing spondylitis.

**Exudates**
Biological fluids that filter from the circulatory system into lesions or areas of inflammation. Exudate is characterized by a high content of plasma proteins, cells and cellular debris. Pus is an example of an exudate found in infected wounds and it contains bacteria and high concentrations of white blood cells.

**Immunoresolvents**
A term that denotes agents that stimulate the resolution of inflammation. Examples include lipoxins, resolvins and protectins.

**Innate lymphoid cells**
Lymphoid cells that do not express unique antigen receptors derived from gene rearrangement or cell-surface markers that are characteristic of other immune cell lineages. However, in response to innate tissue-derived signals, they secrete cytokines that are associated with T helper cell subsets. They can promote protective immunity during infection, but may also have pathological roles in certain diseases.

**Leukotrienes**
A class of eicosanoids derived from arachidonic acid by the action of arachidonate 5-lipoxygenase and downstream enzymes. They have a conjugated triene double-bond structure and various pro-inflammatory activities, including leukocyte activation (in the case of leukotriene B4) and bronchoconstriction (in the case of leukotriene C4 and leukotriene D4).

**Lipoxins**
A class of eicosanoids that are produced by lipoxygenase-mediated metabolism of arachidonic acid. They are trihydroxytetraene-containing structures with potent biological activities in the resolution of inflammation.

**NADPH oxidase**
NADPH oxidases are plasma membrane- and phagosomal membrane-bound enzyme complexes that transfer electrons from NADPH to molecular oxygen, promoting the generation of the reactive oxygen species superoxide.

**Positional memory**
The basis by which cells know their spatial relationship to each other (in terms of top or bottom, left or right and inside or outside) is defined during embryological development. This relative 'positioning' of one cell to another is generally 'remembered' throughout life. However, during tissue pathology (for example, in cancer and during inflammation) positional memory can be lost.

**Prostaglandins**
Cyclopentane-ring-containing lipids derived from the metabolism of arachidonic acid by the action of cyclooxygenases and downstream synthase enzymes. They have a diverse range of biological activities and a well-recognized role in inflammation and pain.

**Protectins**
A family of docosahexaenoic acid-derived mediators characterized by the presence of a conjugated triene double-bond structure and 22 carbons with 6 double bonds.

**Resolvins**
Lipid mediators that are induced in the resolution phase following acute inflammation. They are biosynthesized from the essential omega-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid.

**Type 1 hypersensitivity responses**
Immediate allergic reactions to allergens in previously sensitized individuals. These responses are mediated by pre-existing allergen-specific IgE antibodies, which promote the activation and degranulation of tissue mast cells and basophils in the blood.

*Q The resolution of inflammation is clearly a complex process. Which systems do you think are best suited to studying the mechanisms involved?*

**D.W.G.** In general, anti-inflammatory treatments have been developed on the basis of their ability to inhibit factors that drive acute inflammation. Such therapies include non-steroidal anti-inflammatory drugs (NSAIDs) (which inhibit the early release of prostaglandins) and biologics, such as TNF inhibitors. However, NSAIDs do not inhibit type 1 hypersensitivity responses and allergic reactions. In fact, they are contraindicated in these cases, as such reactions are driven by leukotrienes. NSAIDs are effective analgesics for 'peripheral' pain but are relatively ineffective in treating pain associated with fibromyalgia, which is thought to be 'central'[40].

The point is that the cellular and biochemical processes that initiate and drive host responses to bacterial inflammation, for instance, are different from those involved in mounting reactions to allergens. As a result, it is unlikely that any single pro-resolution strategy will be a panacea for all non-resolving, chronic inflammatory and autoimmune diseases. Indeed, the systems best suited for studying resolution are likely to be tissue, stimulus and phase-of-disease specific. Therefore, when developing a pro-resolution drug strategy for a particular disease that affects a particular organ, one must use, when possible, experimental models and human tissues pertinent to that organ, and stimuli that best replicate the disease of interest. If common pro-resolution pathways exist for diseases of disparate aetiologies, then this will be an added bonus, but we cannot rely on this being the case.

Of course, it is not always possible to accurately model human diseases. Nonetheless, an organ- and stimulus-based systematic approach will maximise our chances of developing an effective pro-resolution drug strategy. Indeed, we now appreciate that diseases such as Crohn's disease and rheumatoid arthritis are complex syndromes with varying aetiologies and progression patterns, which is why TNF blockade, for example, is not effective in all patients with rheumatoid arthritis. Even within a specific disease, there are likely to be divergent pro-resolution processes needed for disease remission.

**P.P.T.** A holistic approach is needed to investigate the mechanisms involved in the resolution of inflammation, integrating animal models of inflammation with human biology. As the factors involved during different stages of inflammation depend on the phase of the disease, there should be an emphasis on mechanistic experimental studies *in vivo* in humans as well as in animal models, complemented by *in vitro* and *ex vivo* models.

The experimental *in vivo* models will allow investigators to study the kinetics of the response on a molecular and cellular level after the experimental induction of inflammation. In addition to established animal models, novel approaches may be used, such as transgenic mice overexpressing human proteins involved in resolving inflammation, or the zebrafish model, which provides a bridge between cell-based assays and mammalian whole-organism models[41]. In human mechanistic studies, inflammation may be induced by the administration of a pro-inflammatory agent or by using non-invasive models, such as the gingivitis model[42]. In addition to molecular studies, a variety of techniques (including immunohistochemistry and *in vivo* imaging of labelled cells) can be applied to assess cell infiltrates, and to investigate the migration, retention, egress and death of cells in the inflamed compartment and the effects of these cells on tissue repair and remodelling.

**C.N.S.** My research group has pondered this question for some time. We now appreciate that anti-inflammatory mediators are not equivalent to mediators with pro-resolving actions. To tease out key resolution responses, we have used histological and cell-trafficking assays, but also models that permit the interrogation of exudates and tissues using a systems approach, in order to achieve both temporal and spatial information[5].

Resolution is not a newly identified process and has been defined histologically for quite some time[17]. However, it is only recently that we have begun to understand the role of resolution mediators in this active process[2,4,5]. Mediators such as prostaglandin E2 have multiple roles both in the initiation phase of inflammation and in the resolution phase. Thus, although they block pro-inflammatory responses, cyclooxygenase 2 (COX2) inhibitors can also delay the resolution of inflammation[43,44]. Those systems that allow us to monitor complete resolution at the tissue level, such as the mouse peritonitis and air-pouch inflammation models, are ideally suited for studying resolution mechanisms, and they permit the temporal and differential interrogation of the mediators and cellular players that are involved[2,45]. A set of indices[45] has been put into place to quantitatively define resolution parameters that are applicable to many tissues and organs[46]. By determining the values of the defined resolution indices, one can pinpoint the mode of action of a test compound and thus determine whether it is a pro-resolving drug. Results from these studies provide clear first steps for decoding the complexities of active resolution programmes.

We have also started to examine the profiles of immune mediators present at the surgical incisions of patients in the operating room. The advantage of this system is that is allows us to start with a fixed time-point 'zero' at the start of surgery[47]. We have taken this approach because of the complexity of classic inflammatory diseases, such as rheumatoid arthritis. In these patients, it is not easy to establish the time point at which the disease was initiated or to assess where natural resolution mechanisms may have failed.

Hopefully, such collaborations with surgeons and dentists in perioperative medicine within and around the operating room will help us to clarify the principles of active resolution programmes and to test new pro-resolving therapies.

**B.S.** As discussed already above, the mechanisms involved in the resolution of inflammation are inherently complex. Despite this, it is preferable to study these mechanisms *in vivo*, taking advantage of the wide range of inflammation models in mice and perhaps starting with more simplistic models of inflammation that are induced by TLR agonists. A very promising model may be the relatively new imiquimod-induced model of psoriasis-like disease in mice. Topical application of this TLR7 agonist over a period of 5 days results in fulminant skin inflammation, which is, however, very rapidly resolved. Nothing is known currently about the resolution programme in this model.

**C.D.B.** I think it is important to add that, despite compelling evidence that dysregulation of pro-inflammatory pathways contributes to the pathogenesis of many chronic inflammatory diseases, there remains little hard genetic or, indeed, pharmacological evidence to suggest that the dysregulation of pro-resolution pathways also promotes chronic inflammation. However, careful genetic studies that look at the biological consequences of the loss of pro-resolving genes are likely to be informative here.

As mentioned by P.P.T., further use of genetically modified mice and other model organisms, such as zebrafish, combined with biochemical and molecular pathway analyses, is likely to shed new light on the biology of resolution[48].

It is also very likely that the application of unbiased polyomic approaches (that is, genome, proteome, lipidome and metabolome analyses) in experimental and clinical studies will unveil important new findings. A major challenge for both the pharmaceutical and the academic sector will be to develop a coordinated and systematic approach to explore the interrelationships between immune function, inflammation, tissue damage and tissue repair in inflammatory diseases in humans. This will require a step change in the way in which clinical studies are designed, as they will need to capture data on clinically meaningful indices of resolution. There is also a pressing need to re-evaluate how experimental models are used to establish causality and test pharmacological interventions with pro-resolving agents in human disease. Key to success, however, will be the documentation of precise kinetic events during the inflammatory process and their temporal relationship to the persistence or resolution of inflammation, particularly in humans *in vivo*.

**Q** *What clinical advantages would new therapies that actively promote the resolution of inflammation offer over existing therapies that target pro-inflammatory mediators?*

**P.P.T.** Even for conditions in which there has been significant progress, such as in the treatment of rheumatoid arthritis, the reality is that most patients do not achieve complete remission of the disease, despite the armamentarium of available anti-inflammatory therapies. As the goal should be to induce remission, or preferably cure, in all patients, an integrated approach is needed that blocks pro-inflammatory pathways as well as actively promoting the resolution of inflammation; these strategies are not mutually exclusive. The therapeutic approach should preferably be designed for an individual patient in the context of a personalized healthcare approach.

What is the advantage of actively promoting the resolution of inflammation? First, the stimulation of anti-inflammatory pathways, in combination with other approaches, may be needed to achieve the goal of a cure. Second, it is conceivable that an approach targeting the endogenous pathways that control inflammation would be safer and better tolerated than existing anti-inflammatory therapies, although this remains to be shown. Third, mechanisms involved in the resolution of inflammation could also promote tissue repair and remodelling. For instance, chloride intracellular channel protein 4 (CLIC4) — an integral component of the transforming growth factor-β (TGFβ) signalling pathway — is highly upregulated in skin wounds and has a crucial role in skin healing and corneal wound re-epithelialization[49]. Fourth, it is very likely that the use of more 'natural' mechanisms will be very appealing to patients, as illustrated by the attractiveness of alternative medicines as well as by my recent experiences in an experimental study. In this study, we implant a device that stimulates the vagus nerve into patients with active rheumatoid arthritis. We are currently evaluating whether such stimulation of the endogenous cholinergic anti-inflammatory pathway can improve clinical manifestations of rheumatoid arthritis.

**C.N.S.** Agents that target pro-inflammatory mediators have dominated the pharmacopoeia for inflammatory diseases for more than 100 years. Although many existing therapies are very useful, they evoke some unwanted effects. For example, TNF-specific antibody therapy is associated with increased susceptibility to infections. Now, with resolution indices[45], many currently used agents are quantified for their impact on natural resolution[46]. NSAIDs and lipoxygenase inhibitors delay resolution at the tissue level even though they reduce signs of inflammation (namely, redness and swelling).

The advantages of immunoresolvents would be that they could stop or limit further PMN recruitment, counter-regulate pro-inflammatory mediators and enhance the containment and phagocytosis of cellular debris and apoptotic neutrophils. Therapies that actively promote resolution may also have the advantage of enhancing innate immune responses to bacterial infections[21]. For example, resolvins, protectins and lipoxins limit inflammation but also enhance the ability of phagocytes to engulf and kill bacteria.

Importantly, we may not necessarily have to develop new drugs to promote resolution; for instance, glucocorticoids and aspirin can enhance resolution[43,50]. Glucocorticoids stimulate the release of annexin 1, which contains a peptide that activates the lipoxin A4 receptor (ALX; also known as FPR2), and aspirin triggers the biosynthesis of endogenous 15-epi-lipoxin A4, which also activates ALX[3]. Together, these drugs have the ability to promote the resolution process by triggering ALX on phagocytes, which leads to the activation of specific endogenous resolution and anti-inflammatory mechanisms[43,50]. Specific kinase inhibitors[51] and *N*-arachidonoyl glycine[52] may also be able to initiate resolution responses.

In my opinion, new therapeutics that stimulate resolution would have the benefit of not rendering patients immunosuppressed. They would not prolong the persistence of inflammatory cells at affected tissue sites but, instead, would stimulate tissue regeneration[12]. For example, maresin 1 and resolvin E1 both stimulate tissue regeneration in planaria flatworms[12]. Also, protectin D1 and lipoxin A4 have been shown to simulate the proliferation and differentiation of stem cells[53], which may help to promote tissue repair. All of these are desirable steps for catabasis (that is, successful resolution) and a return to homeostasis.

**C.D.B.** Current anti-inflammatory therapies control the cardinal signs of inflammation (namely, heat, swelling, pain, redness and loss of function). Most antagonize pro-inflammatory pathways that are induced when acute inflammatory responses begin. Embracing resolution therapeutically will require a shift in emphasis from inhibitory therapy to replacement therapy (that is, a switch from antagonism to agonism). In fact, some anti-inflammatory agents may even be 'resolution toxic'. For example, the inhibition of COX2 is helpful in that it decreases the production of pro-inflammatory prostaglandins, but less desirably it also blocks the production of prostaglandin E2 and prostaglandin D2, which have important roles in bringing about the resolution of inflammation[44].

Currently, no drugs have been specially designed to induce pro-resolving pathways, although compounds that target apoptotic pathways have shown potential[51]. There has been no attempt to directly measure a clinically meaningful 'resolution or repair index', despite such indices being developed in animal models of acute resolving inflammation[13], as described by C.N.S. above. This represents a major 'blind spot' in current research strategies that target inflammation. There are drugs that mediate their effects, at least in part, by triggering the synthesis of endogenous anti-inflammatory mediators. For example, methotrexate and FK506 are thought to exert their effects by increasing the synthesis of adenosine, which acts through the A2A adenosine receptor to control leukocyte trafficking (for a review see REF. 13).

An ideal drug would be able to blunt an inflammatory response and also activate the resolution programme. As C.N.S. mentions, such drugs already exist. Glucocorticoids, in addition to having anti-inflammatory properties, also promote the resolution of inflammation, and aspirin 'jump-starts' the resolution response by generating 15*R*-epimers of lipoxins as well as 17*R*-epimers of resolvins and protectins. However, these drugs have major side effects and are not 'clean resolvers'. The advantage of purely pro-resolution agonists is that they might not mediate the 'friendly fire' that steroids and aspirin exert on the immune and vascular systems, respectively. The disadvantage is that they may terminate the inflammatory programme prematurely, before it has had time to mediate sufficient tissue repair[4].

Therefore, the clinical use of pro-resolving compounds will require a careful analysis to establish the appropriate 'time from insult' for intervention. Such an analysis in humans is still in its infancy, especially as the causative agents of many chronic inflammatory diseases remain unknown. However, exciting advances are being made in conditions such as rheumatoid arthritis, in which the relationships between genetic, environmental and immunological risks are now much clearer[54].

**D.W.G.** In general, as discussed by P.P.T. and C.D.B. above, most chronic inflammatory diseases would benefit from a dual strategy of anti-inflammation (dampening the pro-inflammatory factors that perpetuate the disease) and pro-resolution. However, there is a concern that prematurely terminating responses to infection, for instance, could be detrimental to the host. After all, inflammation is a good thing — it's when it goes into disarray that trouble begins.

Furthermore, achieving bacterial clearance with a treatment that dampens inflammation appears to be inconsistent with the primordial objective of host defence. However, in response to infection, prostaglandin E2 elevates cellular levels of cyclic AMP, which, in turn, dampens NADPH oxidase-mediated bacterial killing as well as Fcγ receptor-mediated phagocytosis[55,56]. Therefore, even though NSAIDs inhibit acute inflammation, their net effect on infection is enhanced bacterial clearance arising from their inhibition of immune-suppressive prostaglandin E2 (REF. 57).

The link between anti-inflammatory responses and antibacterial ones is also exemplified in prostaglandin E receptor EP3-deficient mice, which show enhanced pulmonary clearance of *Streptococcus pneumoniae* together with an impaired febrile response to infection and a concomitant reduction in the accumulation of neutrophils in the lungs[58]. The reconciliation of pro-resolution and antibacterial responses can be seen in a caecal ligation and puncture model when the mice are treated with resolvin D2. This therapy decreases local and systemic bacterial loads and cytokine production and increases mouse survival rates, despite reducing neutrophil trafficking into the peritoneum[59]. Moreover, treating mice with resolvin E1 in a model of aspiration pneumonia decreased neutrophil accumulation in the lungs by 55%, and also reduced the levels of cytokines and chemokines, but enhanced the clearance of *Escherichia coli*[60]. Therefore, anti-inflammatory and pro-resolution responses can coexist, albeit counter-intuitively, with efficient bacterial killing. This leaves the door open, conceptually, for the development of therapies that are both anti-inflammatory and pro-resolution in nature.

**B.S.** I am not sure that it will be feasible to replace anti-inflammatory strategies with pro-resolution ones. In a dysregulated chronic inflammatory response, it would seem to me essential to first target rampant inflammation before there is any chance of pro-resolution mediators taking effect. However, as suggested already, perhaps combination therapies will be the way forward.

**C.N.S.** Now that the door is wide open for approaching resolution as a new area for therapeutics, we of course require more preclinical and clinical research to expand our appreciation of the potential for this new area. But already a recent clinical trial has shown that topical treatment with a pro-resolving mediator — an aspirin-triggered lipoxin A4 analogue — by itself effectively reduced the severity of infant eczema to a similar extent as steroid therapy in a double-blind placebo-controlled clinical trial[61]. These findings suggest that, at least for some inflammatory diseases, pro-resolving mediators could be as effective as anti-inflammatory drugs and may not have some of the harmful side effects.

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1. Gilroy, D. W., Lawrence, T., Perretti, M. & Rossi, A. G. Inflammatory resolution: new opportunities for drug discovery. *Nature Rev. Drug Discov.* **3**, 401–416 (2004).
2. Serhan, C. N. *et al.* Resolvins: a family of bioactive products of omega-3 fatty acid transformation circuits initiated by aspirin treatment that counter proinflammation signals. *J. Exp. Med.* **196**, 1025–1037 (2002).
3. Gilroy, D. W. & Perretti, M. Aspirin and steroids: new mechanistic findings and avenues for drug discovery. *Curr. Opin. Pharmacol.* **5**, 405–411 (2005).
4. Serhan, C. N. & Savill, J. Resolution of inflammation: the beginning programs the end. *Nature Immunol.* **6**, 1191–1197 (2005).
5. Serhan, C. N. A search for endogenous mechanisms of anti-inflammation uncovers novel chemical mediators: missing links to resolution. *Histochem. Cell Biol.* **122**, 305–321 (2004).
6. Frazier, W. J. *et al.* Increased inflammation, impaired bacterial clearance, and metabolic disruption after Gram-negative sepsis in Mkp-1-deficient mice. *J. Immunol.* **183**, 7411–7419 (2009).
7. Olofsson, P. S., Rosas-Ballina, M., Levine, Y. A. & Tracey, K. J. Rethinking inflammation: neural circuits in the regulation of immunity. *Immunol. Rev.* **248**, 188–204 (2012).
8. Metchnikoff, E. *Immunity in Infective Diseases* (Cambridge Univ. Press, 1905).
9. Tauber, A. I. & Chernyak, L. *Metchnikoff and the Origins of Immunology: From Metaphor to Theory* (Oxford Univ. Press, 1991).
10. Savill, J. S., Henson, P. M. & Haslett, C. Phagocytosis of aged human neutrophils by macrophages is mediated by a novel "charge-sensitive" recognition mechanism. *J. Clin. Invest.* **84**, 1518–1527 (1989).
11. Serhan, C. N. *et al.* Novel functional sets of lipid-derived mediators with antiinflammatory actions generated from omega-3 fatty acids via cyclooxygenase 2–nonsteroidal antiinflammatory drugs and transcellular processing. *J. Exp. Med.* **192**, 1197–1204 (2000).
12. Serhan, C. N. *et al.* Macrophage pro-resolving mediator maresin 1 stimulates tissue regeneration and controls pain. *FASEB J.* **26**, 1755–1765 (2012).
13. Serhan, C. N. *et al.* Resolution of inflammation: state of the art, definitions and terms. *FASEB J.* **21**, 325–332 (2007).
14. Mitchell, S. *et al.* Lipoxins, aspirin-triggered epi-lipoxins, lipoxin stable analogues, and the resolution of inflammation: stimulation of macrophage phagocytosis of apoptotic neutrophils *in vivo*. *J. Am. Soc. Nephrol.* **13**, 2497–2507 (2002).
15. Lawrence, T., Gilroy, D. W., Colville-Nash, P. R. & Willoughby, D. A. Possible new role for NF-κB in the resolution of inflammation. *Nature Med.* **7**, 1291–1297 (2001).
16. Hyman, M. C. *et al.* Self-regulation of inflammatory cell trafficking in mice by the leukocyte surface apyrase CD39. *J. Clin. Invest.* **119**, 1136–1149 (2009).

17. Majno, G. & Joris, I. *Cells, Tissues and Disease: Principles of General Pathology* (Blackwell Science, 1996).
18. Yamada, T. *et al.* Eosinophils promote resolution of acute periotonitis by producing proresolving mediators in mice. *FASEB J.* **25**, 561–568 (2011).
19. Haworth, O., Cernadas, M., Yang, R., Serhan, C. N. & Levy, B. D. Resolvin E1 regulates interleukin 23, interferon-γ and lipoxin A4 to promote the resolution of allergic airway inflammation. *Nature Immunol.* **9**, 873–879 (2008).
20. Ariel, A. *et al.* The docosatriene protectin D1 is produced by $T_H2$ skewing and promotes human T cell apoptosis via lipid raft clustering. *J. Biol. Chem.* **280**, 43079–43086 (2005).
21. Chiang, N. *et al.* Infection regulates pro-resolving mediators that lower antibiotic requirements. *Nature* **484**, 524–528 (2012).
22. Uderhardt, S. *et al.* 12/15-lipoxygenase orchestrates the clearance of apoptotic cells and maintains immunologic tolerance. *Immunity* **36**, 834–846 (2012).
23. Rajakariar, R. *et al.* Novel biphasic role for lymphocytes revealed during resolving inflammation. *Blood* **111**, 4184–4192 (2008).
24. Didierlaurent, A. *et al.* Sustained desensitization to bacterial Toll-like receptor ligands after resolution of respiratory influenza infection. *J. Exp. Med.* **205**, 323–329 (2008).
25. Duffield, J. S. *et al.* Selective depletion of macrophages reveals distinct, opposing roles during liver injury and repair. *J. Clin. Invest.* **115**, 56–65 (2005).
26. Stables, M. J. *et al.* Transcriptomic analyses of murine resolution-phase macrophages. *Blood* **118**, e192–e208 (2012).
27. Fang, Y., Sharp, G. C., Yagita, H. & Braley-Mullen, H. A critical role for TRAIL in resolution of granulomatous experimental autoimmune thyroiditis. *J. Pathol.* **216**, 505–513 (2008).
28. Buckley, C. D. *et al.* Fibroblasts regulate the switch from acute resolving to chronic persistent inflammation. *Trends Immunol.* **22**, 199–204 (2001).
29. Parsonage, G. *et al.* A stromal address code defined by fibroblasts. *Trends Immunol.* **26**, 150–156 (2005).
30. Sherlock, J. P. *et al.* IL-23 induces spondyloarthropathy by acting on ROR-γt$^+$ CD3$^+$CD4$^-$ CD8$^-$ entheseal resident T cells. *Nature Med.* **18**, 1069–1076 (2012).
31. van Maanen, M. A., Stoof, S. P., Larosa, G. J., Vervoordeldonk, M. J. & Tak, P. P. Role of the cholinergic nervous system in rheumatoid arthritis: aggravation of arthritis in nicotinic acetylcholine receptor α7 subunit gene knockout mice. *Ann. Rheum. Dis.* **69**, 1717–1723 (2010).
32. Cutolo, M., Foppiani, L. & Minuto, F. Hypothalamic–pituitary–adrenal axis impairment in the pathogenesis of rheumatoid arthritis and polymyalgia rheumatica. *J. Endocrinol. Invest.* **25**, 19–23 (2002).
33. McGettrick, H. M., Butler, L. M., Buckley, C. D., Rainger, G. E. & Nash, G. B. Tissue stroma as a regulator of leukocyte recruitment in inflammation. *J. Leukoc. Biol.* **91**, 385–400 (2012).
34. Tak, P. P., Zvaifler, N. J., Green, D. R. & Firestein, G. S. Rheumatoid arthritis and p53: how oxidative stress might alter the course of inflammatory diseases. *Immunol. Today* **21**, 78–82 (2000).
35. Murdoch, J. R. & Lloyd, C. M. Resolution of allergic airway inflammation and airway hyperreactivity is mediated by IL-17-producing γδ T cells. *Am. J. Respir. Crit. Care Med.* **182**, 464–476 (2010).
36. Torchinsky, M. B., Garaude, J., Martin, A. P. & Blander, J. M. Innate immune recognition of infected apoptotic cells directs $T_H17$ cell differentiation. *Nature* **458**, 78–82 (2009).
37. Segal, A. W., Geisow, M., Garcia, R., Harper, A. & Miller, R. The respiratory burst of phagocytic cells is associated with a rise in vacuolar pH. *Nature* **290**, 406–409 (1981).
38. Pollock, J. D. *et al.* Mouse model of X-linked chronic granulomatous disease, an inherited defect in phagocyte superoxide production. *Nature Genet.* **9**, 202–209 (1995).
39. Calabro, S. *et al.* Vaccine adjuvants alum and MF59 induce rapid recruitment of neutrophils and monocytes that participate in antigen transport to draining lymph nodes. *Vaccine* **29**, 1812–1823 (2011).
40. Dadabhoy, D. & Clauw, D. J. Therapy insight: fibromyalgia — a different type of pain needing a different type of treatment. *Nature Clin. Pract. Rheumatol.* **2**, 364–372 (2006).
41. Brittijn, S. A. *et al.* Zebrafish development and regeneration: new tools for biomedical research. *Int. J. Dev. Biol.* **53**, 835–850 (2009).
42. Chapple, I. L., Socransky, S. S., Dibart, S., Glenwright, H. D. & Matthews, J. B. Chemiluminescent assay of alkaline phosphatase in human gingival crevicular fluid: investigations with an experimental gingivitis model and studies on the source of the enzyme within crevicular fluid. *J. Clin. Periodontol.* **23**, 587–594 (1996).
43. Chan, M. M.-Y. & Moore, A. R. Resolution of inflammation in murine autoimmune arthritis is disrupted by cyclooxygenase-2 inhibition and restored by prostaglandin E2-mediated lipoxin A4 production. *J. Immunol.* **184**, 6418–6426 (2010).
44. Gilroy, D. W. *et al.* Inducible cyclooxygenase may have anti-inflammatory properties. *Nature Med.* **5**, 698–701 (1999).
45. Bannenberg, G. L. *et al.* Molecular circuits of resolution: formation and actions of resolvins and protectins. *J. Immunol.* **174**, 4345–4355 (2005).
46. Navarro-Xavier, R. A. *et al.* A new strategy for the identification of novel molecules with targeted proresolution of inflammation properties. *J. Immunol.* **184**, 1516–1525 (2010).
47. Pillai, P. S. *et al.* Chemical mediators of inflammation and resolution in post-operative abdominal aortic aneurysm patients. *Inflammation* **35**, 98–113 (2012).
48. Mulero, V., Sepulcre, M. P., Rainger, G. E. & Buckley, C. D. Editorial: neutrophils live on a two-way street. *J. Leukoc. Biol.* **89**, 645–647 (2011).
49. Padmakumar, V. C. *et al.* Spontaneous skin erosions and reduced skin and corneal wound healing characterize CLIC4$^{NULL}$ mice. *Am. J. Pathol.* **181**, 74–84 (2012).
50. Perretti, M. *et al.* Endogenous lipid- and peptide-derived anti-inflammatory pathways generated with gluco-corticoid and aspirin treatment activate the lipoxin A4 receptor. *Nature Med.* **8**, 1296–1302 (2002).
51. Rossi, A. G. *et al.* Cyclin-dependent kinase inhibitors enhance the resolution of inflammation by promoting inflammatory cell apoptosis. *Nature Med.* **12**, 1056–1064 (2006).
52. Burstein, S. H., McQuain, C. A., Ross, A. H., Salmonsen, R. A. & Zurier, R. E. Resolution of inflammation by *N*-arachidonoylglycine. *J. Cell. Biochem.* **112**, 3227–3233 (2011).
53. Yanes, O. *et al.* Metabolic oxidation regulates embryonic stem cell differentiation. *Nature Chem. Biol.* **6**, 411–417 (2010).
54. Gerlag, D. M. *et al.* EULAR recommendations for terminology and research in individuals at risk of rheumatoid arthritis: report from the Study Group for Risk Factors for Rheumatoid Arthritis. *Ann. Rheum. Dis.* **71**, 638–641 (2012).
55. Serezani, C. H. *et al.* Prostaglandin E2 suppresses bacterial killing in alveolar macrophages by inhibiting NADPH oxidase. *Am. J. Respir. Cell Mol. Biol.* **37**, 562–570 (2007).
56. Aronoff, D. M., Canetti, C. & Peters-Golden, M. Prostaglandin E2 inhibits alveolar macrophage phagocytosis through an E-prostanoid 2 receptor-mediated increase in intracellular cyclic AMP. *J. Immunol.* **173**, 559–565 (2004).
57. Stables, M. J. *et al.* Priming innate immune responses to infection by cyclooxygenase inhibition kills antibiotic-susceptible and -resistant bacteria. *Blood* **116**, 2950–2959 (2010).
58. Aronoff, D. M. *et al.* E-prostanoid 3 receptor deletion improves pulmonary host defense and protects mice from death in severe *Streptococcus pneumoniae* infection. *J. Immunol.* **183**, 2642–2649 (2009).
59. Spite, M. *et al.* Resolvin D2 is a potent regulator of leukocytes and controls microbial sepsis. *Nature* **461**, 1287–1291 (2009).
60. Seki, H. *et al.* The anti-inflammatory and proresolving mediator resolvin E1 protects mice from bacterial pneumonia and acute lung injury. *J. Immunol.* **184**, 836–843 (2010).
61. Wu, S. H., Chen, X. Q., Liu, B., Wu, H. J. & Dong, L. Efficacy and safety of 15(*R*/*S*)-methyl-lipoxin $A_4$ in topical treatment of infantile eczema. *Br. J. Dermatol.* 27 Jul 2012 (doi:10.1111/j.1365-2133.2012.11177.x).



**Competing interests statement**
The authors declare competing financial interests: see Web version for details.


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