Therapeutic Thought

With most therapies being essentially symptomatic, the industry should look to complement immunotherapy to transform the management of autoimmunity. This approach is currently the focus in oncology pipelines, but hesitation remains due to its history and complexity

Cedric Francois and Pascal Deschatelets at Apellis Pharmaceuticals

Recent years have been witness to a landslide shift in oncology therapeutics. In the second half of the 20th century, the primary goal of anti-cancer therapies was to kill as many cancer cells as possible, with chemotherapy and radiotherapy representing the cornerstones of this approach. The first decade of the 21st century saw the emergence of anti-angiogenesis as a viable strategy, which involves preventing the growth of blood vessels needed to supply tumours and was the centre point of many promising therapies.

Now, the second decade is shaping up to become the era of immunotherapy. In a mere few years, most major pharmaceutical companies with programmes in oncology have made immunotherapy a focal point of their pipeline, and seemingly every week new data emerge indicating that it is possible to 'correct' a permissive immune system into properly eliminating tumours.

Consequence of Dysfunction?

Immunotherapy in oncology hinges on the premise that cancer is a disease of immune dysfunction. The human body is made up of approximately 37 trillion cells. Statistically, many of these cells mutate and become dysplastic or cancerous at any given time, but our immune system ensures that defective cells are eliminated before they have the ability to organise themselves into tumors. If cancer is the consequence of immune dysfunction, then correcting immune dysfunction could theoretically eliminate cancer.

The first indications that manipulating the immune system could be a functional treatment paradigm for cancer emerged a century ago. German doctors W Busch and F Fehleisen observed that certain tumours spontaneously regressed when cancer patients became accidentally infected with *Streptococcus pyogenes* during hospitalisation (1).

Simultaneously, in New York, at what would later become the Memorial Sloan-Kettering Cancer Center, the American doctor William Coley noted that a patient suffering from neck cancer recovered following a similar infection. Towards the end of the 19th century, Dr Coley was using heat-inactivated *S. pyogenes* and *Serratia marcescens* to treat a variety of cancers, including sarcomas, carcinomas, lymphomas, melanomas and myelomas (2-4). Based on his pioneering work, many consider William Coley to be the father of cancer immunotherapy.

Road to Recognition

In spite of these early discoveries, however, it still took well over a century before immunotherapy was rightfully recognised as a viable cancer therapy approach. In the 1990s, two important drug targets gained interest with developers: the interaction between checkpoint inhibitors CTLA-4, and its ligands CD-80 and CD-86; and, more recently, between programmed cell death protein 1 (PD-1), and its receptors, programmed death ligands 1 and 2 (PD-L1/2). Today, thanks to these efforts, physicians are able to induce complete and durable remissions in historically lethal cancers, such as metastatic melanoma.

The importance of these findings, outside of their evident benefits to patients, also resides in our improved understanding of immunology. Until recently, immunology was a field focused on secondary lymphoid organs (spleen and lymph nodes). There was a rather simplistic understanding of how the adaptive immune system is orchestrated, of the variety and plasticity of cell populations involved in immunity, and of the locations where immune responses are coordinated. Most importantly, the importance of the local, tissue-resident immune micro-environment was under-appreciated.

Beyond the promise of cancer immunotherapy as a strategy to alter the local micro-environment in a tumour, immunotherapy holds the potential to correct the micro-environment in tissues where immune dysregulation can be held responsible for a host of diseases – including many, if not most, autoimmune conditions.

Autoimmune Therapies

If killing cancer cells was the primary objective of oncology therapies, then suppressing the immune system has historically been the objective of autoimmune therapies. Corticosteroids

best exemplify how suppressing the effector arms of the immune system can be beneficial in defeating the undesirable effects of inappropriate immune activation. However, the long-term use of immune suppressants leads to a host of side-effects, sometimes worse than those caused by the condition they are intended to treat. The next generation of therapeutics in autoimmunity should aim to correct inappropriate immune behaviour, rather than suppressing it.

Immune correction in autoimmunity should, if anything, be more intuitive than it is in cancer. However, like in cancer, correcting inappropriate immune activation in autoimmunity has proven exceedingly difficult. The immune system has multiple redundant bypass pathways – this is beneficial, and likely vital to a well-functioning adaptive immune system. However, the same redundancy becomes a liability when the immune system malfunctions. There are 36 known interleukins and countless cytokines, prostaglandins, chemokines, anaphylotoxins and other immune factors that foster communication between the many cell populations of the immune system. They are accompanied by a finely-tuned collection of intracellular pathways.

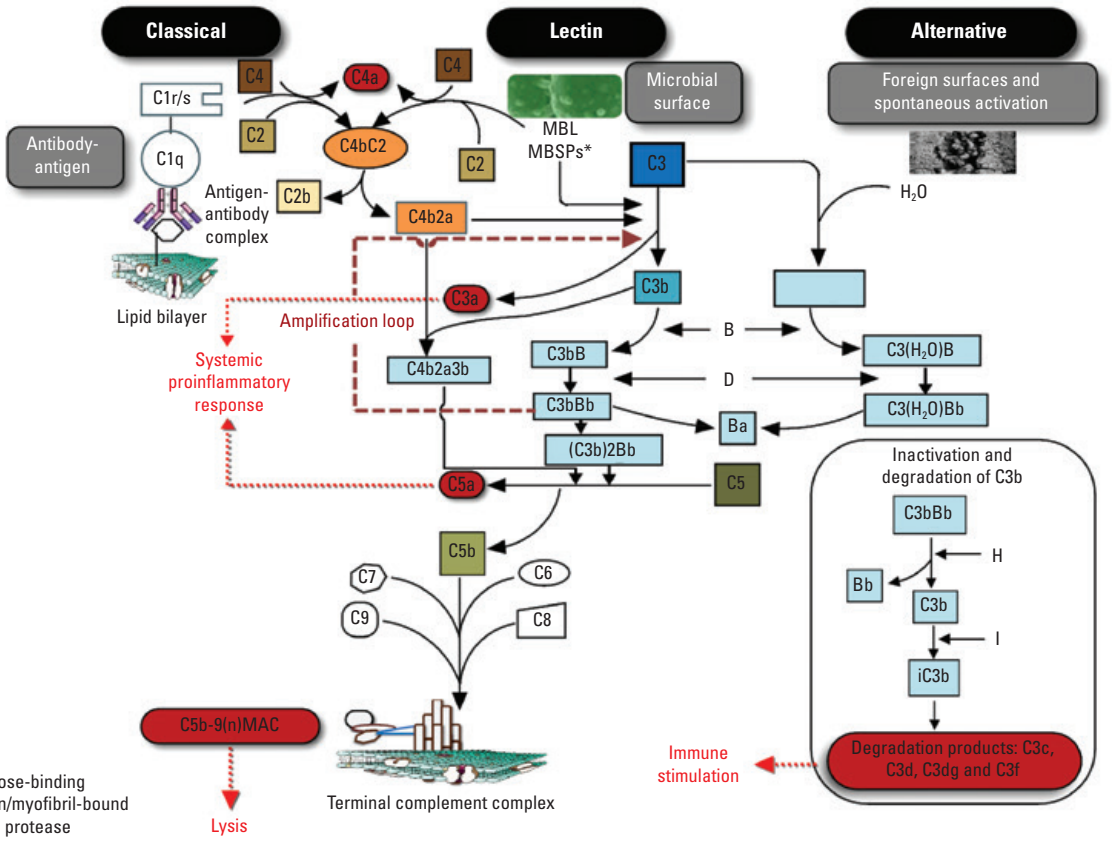
The Complement System

Within the complexity of the adaptive immune system exists the complement system. This system is centred around a protease cascade that has been largely preserved for hundreds of millions of years. It shares many similarities with the coagulation pathway (including significant cross-talk between the two systems), and was the human defence mechanism until we developed the adaptive immune system.

Complement is non-specific and can be activated via three pathways, by a multitude of elements ranging from antibodies to various types of pathogenic by-products, such as lipopolysaccharide or foreign surfaces (see Figure 1). The effector arms of complement can be artificially separated into two pathways: a cell-surface route that culminates in the formation of the so-called membrane attack complex (MAC); and a primarily fluid-phase one that plays a pivotal role in immune modulation. MAC is a protein system that pierces holes in the cell surface. Prokaryotic cells, unlike eukaryotic, are particularly sensitive to MAC formation; however, under certain circumstances, eukaryotic cells can also undergo lysis when exposed to MAC.

The fluid-phase acts through several anaphylotoxins and cascade by-products that influence the behaviour of many adaptive immune cells, including T cells and antigen-presenting cells (APCs). The importance of this modulation should be considered in the context of the evolution of the adaptive immune system, which took place while complement stood back. Recently, intracellular pathways of complement activation with a critical role in adaptive immunity have been uncovered.

Figure 1: The complement pathways



These pathways will undoubtedly reveal many until now unknown and important roles for complement in immune modulation (5).

Lack of Inhibitors

Considering the omnipresence of complement in the body; the high concentration of complement components produced and maintained at significant energy cost; and complement's association with a long list of immune conditions, one would expect it to be a key target for immune modulation. However, in spite of its importance, only two complement inhibitors have made it to market. These are Alexion's Soliris® and Shire's Cinryze, and they are primarily used to prevent haemolysis in diseases where red blood cells are overly sensitive to MAC formation, or in order to inhibit inflammation through cross-talk with the bradykinin pathway.

There are many possible explanations for the lack of approved drugs targeting the complement system, but the main reasons can be summarised as follows:

Fear of Opportunistic Infections
Complement inhibition can expose animals and individuals to infections, particularly *Neisseria meningitides*. This undesirable side-effect has been well-known and described in both patients with complement deficiencies and those treated with Soliris. Experience with Soliris has shown that patients can be effectively vaccinated against the most serious risk, but the severity of potential infections can be intimidating for drug developers.

History
The first complement inhibitors, developed as early as the 1970s, were small-molecule protease inhibitors, often with low specificity and significant toxicity – in part, due to off-target effects in the coagulation pathways. Most companies felt intimidated by these early failures until the 1990s, when a few tried to develop biologicals as a novel way of targeting the complement pathways.

Alexion emerged from those early efforts to become the giant of complement inhibition it is today. However, it was a difficult path that involved considerable failures. Most importantly, the indication for Alexion's Soliris – that ultimately gained market approval – relied on the rather simple mechanism of MAC inhibition, and not on modulating adaptive immunity.

Complexity
Our knowledge and understanding of the complement cascade continues to be limited; the secrets of this incredibly complex and old pathway remain guarded. Drug development's greatest enemy is the unexpected, and the uncertainty surrounding the safety and efficacy of this approach have hampered efforts to develop therapies targeting complement.

Remaining Positive

In spite of these negative elements, a few factors provide encouragement to those studying complement inhibition in patients suffering from autoimmune conditions:

Regulatory Action
Complement is undoubtedly one of the most important danger signals of adaptive immunity. Conceptually, rather than trying to inhibit individual factors within a highly redundant system, it makes sense to remove the primary barometer of danger, and rely on its regulatory action within the adaptive immune system to reset the latter into a well-regulated state.

Symptomology Protection
While Soliris is only a partial inhibitor of complement and might not be ideal to modulate adaptive immunity, it is currently being developed as a treatment for the autoimmune conditions neuromyelitis optica (NMO) and myasthenia gravis (MG). In both those indications, Soliris has shown remarkable and unexpected effects in clinical trials. Rather than functioning as a symptomatic protector against MAC, patients receiving Soliris treatment during a limited period of time (four months for MG and one year for NMO) were protected against symptomatology for months, possibly years, after cessation of treatment – urging the questions: can complement inhibition correct autoimmunity? And, if so, by which mechanism?

C3 Inhibition
While Soliris inhibits complement at the level of complement C5, certain other drugs under development – such as Apellis' APL-1 and APL-2 – inhibit the cascade at the level of complement C3, in order to treat paroxysmal nocturnal haemoglobinuria (PNH), age-related macular degeneration (AMD) and chronic obstructive pulmonary disease (COPD). Unlike C5, inhibition of C3 offers comprehensive complement inhibition, and, most notably, blocks fluid-phase complement activation, along with other immune activation effector

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pathways. If proven to be safe, C3 inhibition offers a unique opportunity to study complement immunotherapy in autoimmunity.

A Hypothesis

While PNH, AMD and COPD are seemingly unrelated diseases, they share remarkable mechanistic similarities. All three are so-called Th17 diseases, sharing the imprints of a type of T cell involvement that is known for its steroid resistance; the polyclonal character of immune response driven by tissue-specific antigens; and the characteristic of persisting and worsening long after the initial immune defect. They all possess the features of irreversible disease, often culminating in complete tissue destruction over prolonged periods of time. A possible hypothesis for complement involvement hinges on the presence of a vicious cycle of autoimmunity, driven and sustained by unnecessary activation (see Figure 2).

An initial insult – an infection or any event that results in undue tissue stress or damage – causes an immune imbalance in the APC-T cell axis, creating a highly-oxidative, local micro-environment, rich in inflammatory cytokines (including IL-17, IFNγ, IL-6, IL13, IL-21, IL-22 and IL-23) and several chemokines (including CCL-20). Neutrophils and monocytes are recruited to the tissue, causing further inflammation and oxidation.

This local environment leads to an up-regulation of complement activation, in part via the alternative pathway and initiated through oxidated by-products. Oxidated phospholipids tend to form adducts with proteins and are known to activate the alternative pathway of complement. Notably, the genetic polymorphism in complement factor H – most strongly associated with AMD – has a reduced ability to control this pathway of complement activation (6). However, in many cases, the up-regulation of polyclonal antibodies is associated with Th17 diseases, and it is possible that the classical pathway of complement is likewise involved.

The end result is local up-regulation of complement activation, playing a critical signalling function to the APCs that define the immune phenotype of the tissue by inappropriately sustaining destructive T cell phenotypes (7).

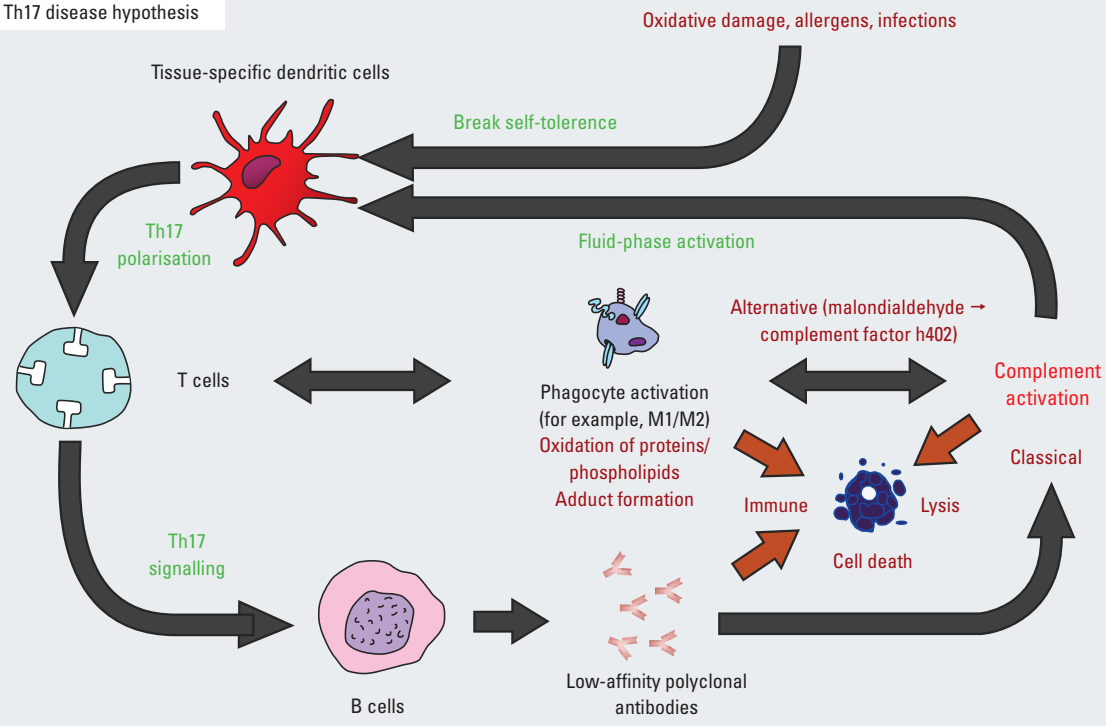
The consequence of this is tissue destruction, mediated by a variety of factors in which macrophages and similar tissue-resident cells, such as microglia, may play an important role. They maintain a detrimental M1/M2 phenotype, as well as sustaining the pathogenic local immune phenotype. It is noteworthy that in wet AMD the predominant macrophage phenotype is pro-angiogenic M2, whereas M1 is dominant in geographic atrophy (8).

Examples of Evidence?

Many marketed drugs affect this hypothetical vicious circle and have been shown to correct autoimmunity in patients. For example, rituximab has been shown, in some cases, to completely resolve bullous pemphigoid – perhaps when the classical pathway is critical, or because patients who respond are genetically more susceptible to classical pathway over-activation.

Campath-1H, as well as anti-thymocyte globulin, can sometimes cure autoimmunity in diseases like aplastic anemia. Another example is how Stelara® can occasionally lead to complete remissions of psoriasis in

Figure 2: Th17 disease hypothesis



patients after a single injection – an effect known to be mediated by IL-23 inhibition and starvation of the Th17 phenotype.

Many, if not all, of these diseases share in common a micro-environment that is suffering from immune imbalance, not dissimilar from cancer but with different consequences. In such micro-environments, cells are inappropriately activated, leading to irreversible (albeit slow) tissue destruction.

Recently, it was discovered that inflammation in areas of atrophy in transplanted organs – with all the imprints of a Th17 disease – is highly correlated with organ failure within two years. Perhaps here, too, complement inhibition could find an important role in breaking the cycle of immune destruction. Indeed, the most distinguishing feature between Th17 diseases, in general, might well be the tissues in which they occur.

Times are Changing

Like in cancer, it is impossible and overly simplistic to categorise autoimmune diseases as a single category of conditions. However, it is worth considering that the history of medicine does not aid our understanding of disease, or the development of innovative therapies.

The classification of diseases is centred on an organic understanding of the human body. Hundreds of years ago – with little other than observation as the tool of medicine – the most logical approach was to classify diseases by the organs in which they occurred. This was the genesis of our current medical hierarchical system, in which we visit ophthalmologists for eye conditions and pulmonologists for lung conditions. This approach to medicine has translated into how we develop drugs, as we try to improve the physical manifestation of diseases (what they 'look' like) in an organ-specific manner. The unfortunate consequence of this outlook is that most current therapies on the market are quintessentially symptomatic.

We are at a turning point in history. With cancer immunotherapy – but also in other fields like stem cell research or with the recent approval of drugs like Sovaldi – we are slowly shifting towards a world in which cures are not only considered desirable, but the only proper way of treating disease. As well as fundamentally impacting quality of life, this redirection will change how pharma companies generate revenue, what patients expect from drugs, and how doctors incorporate therapies into their workflow and daily practice.

Ultimately, this will be a revolution in the most positive of ways, but the regulatory and philosophical adjustment associated with this alteration will neither be easy nor painless. Complement immunotherapy is a therapeutic approach that aims to be mechanistic, organ-agnostic and transformative in the management of autoimmunity. It is one of many immunotherapy approaches that we believe could change the way autoimmunity is treated.

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About the authors

Cedric Francois is co-founder and Chief Executive Officer of Apellis Pharmaceuticals. His primary areas of expertise are immunology and immune system-mediated disease. Cedric received his medical degree from the University of Leuven, Belgium, and his PhD in Physiology from the University of Louisville, US. He is an inventor on many biotechnology patent applications, including all of Potentia's and Apellis' proprietaries. Cedric led Potentia to become the first group to test complement-inhibiting drug candidates for AMD. **Email: cedric@apellis.com**

Pascal Deschatelets co-founded Apellis Pharmaceuticals in 2009 and joined as its Chief Operating Officer (COO). Prior to this, he co-founded Potentia Pharmaceuticals where he also held the position of COO. Pascal has been engaged in state-of-the-art research in the areas of surface chemistry and organic synthesis for the last 25 years, and was a co-founder of Syntetica Fine Chemicals – a custom chemical synthesis company supporting the pharma industry. He received his PhD in Organic Chemistry from the University of Montreal, Canada, and his postdoctoral training at Harvard University, US. **Email: pascal@apellis.com**