Cancer immunotherapy: at a new immune frontier

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Abstract

Cancer immunotherapy has revolutionised survival outcomes in patients to the extent that it is now recognised as one of the major modalities of cancer treatment. Technologies leading the charge are immune checkpoint inhibitory antibodies, chimeric antigen receptor T-cells and recombinant bi-specific T-cell engager molecules. It is thought that their workings depend on their effectiveness on specific immune recognition of cancer cells by cytotoxic T lymphocytes. For immune checkpoint inhibitory antibodies, anti-cancer activity results either from generation of new cytotoxic T lymphocytes specificities or re-invigoration of pre-existing intra-tumoral cytotoxic T lymphocytes. For chimeric antigen receptor T-cells and bi-specific T-cell engagers, genetic engineering re-directs anti-cancer activities of either exogenously delivered T cells or endogenous T cells, respectively. Even so, we must acknowledge the enormous complexity of human immunity and our relatively poor understanding of it. Although our current state of knowledge tells us that combination immunotherapies will be most effective, it does not inform us which combinations will optimise clinical benefit. Consequently, empirical clinical testing of cancer immunotherapies will likely continue in tandem with improved understanding of immunobiological mechanisms of action. Here, we aim to describe key principles of cancer immunotherapy and explain the rationale underlying current use of several different kinds of immune-active agents.

We are witnessing successful use of new immune-active agents that are transforming the face of cancer care. With these agents, we aim to modulate the immune system in order to control the growth of advanced cancers. Immune-active agents may be more effective than many other systemic anti-cancer agents because they can produce long-lasting anti-cancer responses, which in some cases are associated with functional cures. To date, they include immune checkpoint inhibitor (ICI) therapies for an enlarging group of difficult to treat malignancies, and chimeric antigen receptor (CAR) T-cell and recombinant bi-specific T-cell engager therapies for CD19-expressing lymphoid malignancies. An accelerating number of ICIs are gaining worldwide regulatory and reimbursement approvals for relapsed/refractory (r/r) as well as for first and second-line cancer treatment indications (table 1). In late 2017, full US FDA approvals were given for the bi-specific T-cell engager, blinatumumomab, and the CD19-specific CAR T-cell products, tisagenlecleucel (Kymriah™) and axicabtagene ciloleucel (Yescarta™) for r/r cases of acute B-cell lymphoblastic leukaemia (B-ALL) and adult large B-cell lymphoma, respectively.

Together, these technologies have yielded the well-publicised breakthroughs that have made immunotherapy the fourth pillar of anti-cancer treatment, joining the standard modalities of surgery, radiotherapy, and chemotherapy.[1] Moreover, these advances have resulted in a new scientific paradigm, which is now framing new anti-cancer drug development. To the best of our understanding, all of these advances rest on findings that $CD8^+$ cytotoxic T-lymphocytes (CTLs) are primarily

responsible for killing cancer cells.[2-5] ICIs either induce or re-invigorate endogenous cancer antigen-specific T cells. On the other hand, genetic engineering is used in CAR T cells and bi-specific T-cell engagers to re-direct exogenous and endogenous T cells, respectively, toward cancer cell targets.

These new immune-active agents are fundamentally different from other systemic anti-cancer therapies such as cytotoxic drugs and kinase inhibitor drugs, which have mechanisms of action focused on vulnerabilities and drivers in cancer cells. Instead, immune-active agents exploit the distinctive properties of CTLs that then act as living anti-cancer drugs. These distinctive properties include the exquisite specificity and extreme diversity of the CTL antigen receptors and the antigen-specific memory of the subset of long-lived and self-renewing CTLs.

Cancer immunity cycle

The concept of the cancer immunity cycle provides a useful framework to understand cancer immunotherapy, and is based on the architecture of *any* immune response (figure 1). It shows that a consecutive series of events must ensue to enable a productive immune response, including that required for cancer control. Infections of body tissues or tissue damage including that caused by cancer or its treatment initiate an immune response in the 'immunological periphery'. Here, sensing mechanisms carry the information along the afferent arm of the immune response to secondary lymphoid organs such as lymph nodes and spleen. Effective sensing requires cooperation between the innate and adaptive immune systems. In secondary lymphoid organs, immune effector responses are generated and transmitted along the efferent arm of the immune response back to the immunological periphery where invading microorganisms are destroyed and tissue injury is resolved.

Cancers arise from normal body tissues, which are set to a default state of non-reactivity to immunological 'self' (immune tolerance). In contrast, most cancer-specific CTLs react to altered self, which comprises mutation-associated neoantigens.[6,7] An anti-cancer CTL response originates in the lymph nodes draining the cancer. For this to happen, the professional antigen presenting cell (APC), and especially the dendritic cell (DC), which resides as a rare sentinel cell in the immunological periphery, must translocate to the cancer draining lymph nodes. The DC is a highly specialised type of APC and is the only one that can initiate or 'prime' a CTL response. In the periphery, the DC captures and 'processes' cancer-derived material including neoantigens. And 'alarm' or 'danger' signals, which emanate from dead and dying cancer cells, help to stimulate the DC to migrate to the lymph nodes. There, the antigen-laden DC 'presents' the cancer neoantigen to the (cognate) CTL that specifically recognises it. The cellular architecture of lymph nodes is specially organised to maximise the chance of a productive encounter between the neoantigen-bearing APC and its cognate but relatively rare neoantigen-specific CTL. This initial antigen recognition event results in the activation of CTL, which then expands greatly in number to form a clone of cells, each bearing an identical T-cell receptor (TCR) but unique for that clone.[8] During clonal expansion, the CTLs acquire the cytokine secretion profiles and cytotoxic properties that endow them with anti-cancer effector functions upon infiltration into the cancer.

T-cell activation requires conditional signals

T-cell activation is not like a simple 'on' switch but rather relies on a series of inter-related signals which, if conditions are met, enable powerful amplification of the T-cell response. Conversely, if conditions are not met because homeostatic controls, or checkpoints, are dominant, then the T-cell response becomes limited and wanes (figure 2). Signal '1' is the antigen recognition event, and comprises a specific 'lock and key' interaction of the cell-surface peptide-MHC (pMHC) complex with the TCR. These short peptides (9 to 18 amino acid long), which bind the MHC molecules on the surface of cancer cells or APCs, are processed (or proteolytically digested) from antigens within the cell. Signal 1 results in activation of an antigen-specific lymphocyte, which begins to undergo clonal expansion, producing millions of copies if full T-cell activation proceeds.

Signal 2 is the co-stimulation step that is required to complete T-cell activation and to ramp up clonal expansion. If the pMHC complex is presented on a professional APC such as a DC, macrophage, or B cell, then B7.1 (CD80) and B7.2 (CD86) molecules on the APC surface engage the CD28 molecule on the T-cell surface and provide co-stimulation or signal '2' to the T cell. Indeed, there are many other receptor/counter-receptor pairs at the APC-T-cell interface, which modulate co-stimulation and which can be manipulated therapeutically (figure 2).[9]

Without co-stimulation, clonal T-cell expansion is aborted resulting in a state of immunological non-responsiveness. For example, non-haematological cancers can present antigen but they usually do not express co-stimulatory molecules. These cancers appear to hijack the peripheral tolerance mechanism reserved for normal tissues, which as immunological self also do not express co-stimulatory molecules. Nevertheless, if DCs co-exist in the cancer, they can instead take up the cancer neoantigens and present them to antigen-specific lymphocytes. Hence, this process of antigen cross-presentation may compensate for any cancer-intrinsic deficiency of co-stimulatory molecules.[10] On the other hand, an oncogenic driver can prevent the recruitment of the cross-presenting DCs to a cancer, halting the cancer-immunity cycle at its earliest stages even if the cancer has a high load of neoantigens (figure 1).[11]

Finally, in the context of signals 1 and 2, both T cells and APCs secrete additional inflammatory cytokines such as IL-12 or type 1 interferons (IFNs e.g. IFNα/β), which function as signal '3'. Signal 3 facilitates the most efficient expansion of $CD8^+$ CTLs and subsequently their differentiation into fully fledged effector cells with cytolytic capacity and, ultimately, into long-lived memory T cells (figure 2).

Immune checkpoints control T-cell activation

After T-cell activation, T cells also express co-inhibitory receptors, or immune checkpoint molecules, which control the extent and duration of clonal T-cell expansion. The first to be expressed soon after initial T-cell activation is Cytotoxic T-Lymphocyte Antigen-4 (CTLA4). CTLA4 has higher affinity for B7.1 and B7.2 molecules than CD28 and thus out-competes the co-stimulatory signal as well as transmitting its own co-inhibitory signal back into the T cell. Antibody-mediated inhibition of CTLA4 with ipilimumab is most potent during T-cell priming in cancer draining lymph nodes and thus favours the generation and expansion of new antigen-specific T cells.[12] Later, in peripheral non-lymphoid tissues such as cancers, and after T-cell activation, antigen-experienced T cells express the programmed death-1 (PD1) receptor on their cell surface. After PD1 engages with its ligands, PDL1 and PDL2, signalling back from PD1 into the T cell results in de-activation of the CD28 molecule mainly and thus shuts down co-stimulation of T cells (figure 2).

PD1/PDL1 interactions are important for immune homeostasis including the regulation of allergic, anti-infective, and auto-immune responses in most body tissues.[13] It seems that in the tumour microenvironment, cancer and immune cells can hijack the protective physiological function mediated by PDL1 expression. For example, during chronic viral infections, the physiological role of epithelial-cell PDL1 expression is to limit bystander damage to nearby uninfected epithelial cells by the IFNγ-secreting virus-specific $CD8^+$ CTLs. The disruption of immune homeostasis by chronic anti-PD1/PDL inhibitor therapy may help to explain the incidence of immune-related toxicities in nearly every organ system (figure 3).[14-17]

In cancers, both the cancer cells themselves and infiltrating immune cells such as T cells and myeloid cells may express PDL1. Irrespective of whether PDL1 expression is constitutive or inducible, it confers resistance to cancer-specific immune attack. Constitutive PDL1 expression produces innate immune resistance and may result, for example, from chromosomal translocation as in Hodgkin lymphoma. More commonly, IFNγ derived from cancer-specific CTLs induces expression of PDL1 by infiltrating cancer or immune cells and creates adaptive immune resistance.[9] The relief of cancer immune resistance by therapeutic blockade of the PD1/PDL1 axis illustrates most dramatically the unleashed power of the cytotoxic effector activity, which was previously restrained among intratumoral cancer antigen-specific CTLs.[2-5] This effect is most evident after the first cycle of PD1/PDL1 inhibitor therapy when it is manifest as a burst of clonally expanded effector T cells in blood and cancer samples from treated patients.[18,19]

The critical interface between innate and adaptive immunity

The human immune system depends for its effectiveness on bi-directional and self-reinforcing interactions between its innate and adaptive immune subsystems. The innate immune system is evolutionarily ancient. It acts primarily to defend multicellular organisms against invading pathogenic microbes and the DNA-damaging effects of different types of radiation and organic and inorganic chemicals in the external milieu. Consequently, cellular and molecular components of the innate immune system are arrayed at the integumentary barriers of skin and mucosae from which most

carcinomas arise.

The innate immune system responds to external insults in minutes to hours, thus pre-empting the adaptive immune system by preparing for its full activation. To do this, repeated structures on pathogenic microbes and in damaged tissues, which are classified as pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), respectively, bind to structurally invariant pattern recognition receptors (e.g. toll-like receptors) on innate immune cells. Collectively, PAMPs and DAMPs constitute a set of 'danger' signals known as signal '0'.

Dead and dying cancer cells are the main source of DAMPs,[20] which include such key molecules as adenosine tri-phosphate (ATP), cell-surface calreticulin, high mobility group box-1 (HMGB1) protein, and cytosolic DNA and which are markers of immunogenic cell death. Signalling by these molecules activates the innate immune system thus alerting the adaptive immune system. Standard anti-cancer treatments including ionising radiation and cytotoxic drugs, like doxorubicin and oxaliplatin, contribute significantly to immunogenic cell death.[21] Cytosolic DNA stimulates the DNA cytosolic sensing and stimulator of interferon genes (STING) signalling pathway in DCs, resulting in type 1 IFN production, which is associated with cancer infiltration by $CD8^+$ CTLs.[22] As *the* professional APC, the DC integrates a number of PAMP- and DAMP-related inputs as signal 0, which then primes the DC for immune activation (figure 2). Then, as the most efficient antigen processing and presentation machine, the DC has the unique output of priming naïve or antigen-inexperienced T-lymphocytes and so can initiate completely new immune responses.

Conversely, the adaptive immune system operates on a slower timescale of days to weeks. This allows sufficient time for specific molecular recognition, full immune activation and amplified responses that consolidate innate immune responses and result in elimination of targeted microbes and cancers, and resolution of tissue injury. This versatility of the adaptive immune system in large part relies on the extreme diversity of clonal antigen receptors such as the TCR, which in total constitute the immune repertoire available to each individual.

Cells of the innate and adaptive immune subsystems work in concert to help control cancer. For example, *the* professional phagocyte, the macrophage, does not engulf cancer cells if they bear 'don't eat me' signals such as CD47 and PD1, which can be antagonised therapeutically.[23,24] The natural killer cell (NK cell) has a limited repertoire of NK receptors, which can engage certain counter-receptors expressed by metabolically stressed cancer cells, and initiate the death of the cancer cells. Non-malignant cells are exempt from this killing because their expression of MHC class I immune recognition molecules inhibits NK cell-mediated killing.[25,26] On the other hand, CTLs require an arduous training program before they can kill but this training program can result in armoured divisions of CTLs that can kill on a grand scale.

Clinical relevance of this knowledge

For cancers such as leukaemia and glioblastoma with a somatic cancer neoantigen load below the threshold sufficient for effective immune checkpoint blockade,[4,6] the deficient immune elements may be supplied exogenously in the form of CAR-T cells or bi-specific T-cell engager molecules.[4] Conversely, therapeutic endogenous activators of innate and adaptive immunity may favourably alter the tumour microenvironment to enhance anti-cancer immunity and overcome immune escape. These include cytotoxic agents and external or internal ionising radiation, which produce immunogenic cell death, as well as antibody drug conjugates (ADCs), which can not only produce immunogenic cell death but also directly mature DCs.[27] Moreover, oncolytic virotherapy using talimogene laherparepvec (T-Vec) (table 1) is an effective innate immune activator and inducer of immunogenic cell death, and has been a useful complement to ipilimumab in the treatment of metastatic melanoma patients.[28] In all, these agents induce cancer antigen release in vivo and result in auto or in-situ vaccination (figure 1).

Conclusion

Self-evidently, the human immune system is enormously complex, and concepts like the cancer immune set-point have been developed to address this complexity. As illustrated in figure 1, a multitude of different and often tissue-specific cell types engage in manifold endocrine, paracrine and autocrine interactions using many individual cytokines and chemokines, which together help to define

the immune set-point in a given patient. Cancers have been described as ‘wounds that do not heal’,[29] and cytotoxic drugs and ionising radiation may aggravate the tissue injury and chronic inflammation of cancer. These wound healing responses involve stromal cell types such as tumour associated macrophages (TAMs) and myeloid derived suppressor cells (MDSCs) with their associated secretion of molecules such as VEGF, IL-4, IL-10, and TGFβ, which can re-set the cancer immune set-point to create a more immunosuppressive tumour microenvironment (figure 1).[30,31]

This level of manifest complexity has several implications for cancer immunotherapy. The immune system continually applies selection pressures that shape how easily recognised, or not, cancer cells become.[32,33,34] Consequently, cancers may end up not being recognised and their growth will escape immune control, and thus CTL killing. This can happen even during protracted anti-PD1 therapy when genetic defects conferring resistance to immunotherapy can be acquired.[35,36] A cancer functions as an abnormal organ comprised of many different cell types and features such pathological changes as hypoxia, acidosis and necrosis. Nonetheless, a cancer is a robust system that has homeostatic mechanisms that can resist multiple perturbations.[37] In both scenarios, therefore, the combination of therapeutic approaches is most likely to enhance the prospects of durable cancer control.

Acknowledgements
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Table 1: *Approvals of immune-active agents including checkpoint inhibitors by various regulatory agencies worldwide*

Drug	Regulatory Agency	Date of Approval	Cancer Indication
Atezolizumab	USFDA	17 Apr 2017	1L treatment for LA or met urothelial cancer
		18 Oct 2016	2L treatment for met NSCLC
		18 May 2016	2L treatment for LA or met bladder cancer
	EMA	20 Jul 2017	LA or met urothelial carcinoma LA or met NSCLC
	TGA	27 Jul 2017	LA or met NSCLC
Avelumab	USFDA	9 May 2017	LA or met bladder cancer
		3 Apr 2017	Merkel cell carcinoma
	EMA	20 Jul 2017	Merkel cell carcinoma
	TGA	03 Jan 2018	Merkel cell carcinoma
Blinatumomab	USFDA	12 Jul 2017	r/r B-ALL
	EMA	24 Sep 2015	r/r Philadelphia chromosome negative B-ALL
	TGA	9 Nov 2015	r/r Philadelphia chromosome negative B-ALL
Durvalumab	USFDA	16 Feb 2018	unresectable stage III NSCLC not progressing after cCRT
		1 May 2017	LA or met bladder cancer
Ipilimumab	USFDA	25 Mar 2011	met melanoma
		28 Oct 2015	adjuvant treatment for stage 3 melanoma
	EMA	25 Jul 2011	unresectable or met melanoma
	TGA	4 Jul 2011	unresectable or met melanoma
	PBS	Jul 2016	unresectable or met melanoma
Nivolumab	USFDA	20 Dec 2017	Completely resected LA or met melanoma in the adjuvant setting
		22 Sep 2017	HCC previously treated with sorafenib
		31 July 2017	2L treatment for met CRC with MSI-H and dMMR
		2 Feb 2017	2L treatment for LA or met urothelial cancer
		10 Nov 2016	2L treatment for recurrent and met HNSCC
		17 May 2016	r/r cHL
		23 Nov 2015	2L treatment for met RCC
		9 Oct 2015	2L treatment for met non-squamous NSCLC
		4 Mar 2015	2L treatment for met squamous NSCLC
		22 Dec 2014	unresectable or met melanoma
	EMA	2 Jun 2017	unresectable or met urothelial cancer
		23 Mar 2017	2L treatment for HNSCC
		26 Feb 2016	met RCC
		13 Oct 2016	cHL
		25 Feb 2016	LA or met non-squamous NSCLC
		6 Apr 2016	2L treatment for advanced RCC
		20 Jul 2015	advanced squamous NSCLC
		19 June 2015	advanced melanoma
	TGA	16 Feb 2018	2L treatment for unresectable or met UC
		18 Nov 2017	2L treatment for clear cell RCC
		13 Jul 2017	recurrent or met HNSCC
		30 May 2017	r/r cHL
		11 Jan 2016	unresectable or met melanoma
		11 Jan 2016	2L treatment for LA or met squamous NSCLC
	PBS	1 Aug 2017	met clear cell RCC
		1 Aug 2017	LA or met NSCLC
		1 May 2016	unresectable or met melanoma
Nivolumab + Ipilimumab	TGA	11 Jan 2016	unresectable or met melanoma
		1 Oct 2015	

	EMA	May 2016	unresectable or met melanoma without ^{V600}*BRAF* mutation
Pembrolizumab	USFDA	23 Jan 2016	unresectable or met melanoma *across* ^{V600}*BRAF* mutation
		1 Oct 2015	unresectable or met melanoma *without* ^{V600}*BRAF* mutation
		22 Sep 2017	2L treatment for r/r LA met gastric/GEJ adenocarcinoma expressing PDL1
		23 May 2017	1L treatment for MSI high or dMMR met solid tumours
		18 May 2017	met UC
		10 May 2017	1L treatment for met nonsquamous NSCLC irrespective of PD-L1 status
		15 Mar 2017	r/r cHL
		24 Oct 2016	1L treatment for met NSCLC with PD-L1 ≥50%
		5 Aug 2016	recurrent and met HNSCC
		18 Dec 2015	1L treatment for unresectable or met melanoma
		2 Oct 2015	2L treatment for met NSCLC
		4 Sep 2014	2L treatment for unresectable or met melanoma
	EMA	20 July 2017	LA or met UC
		23 Mar 2017	cHL
		15 Dec 2016	1L treatment for met NSCLC with PD-L1 ≥50% without EGFR or ALK mutations
		May 2016	unresectable or met melanoma *without* ^{V600}*BRAF* mutation
		23 Jun 2016	2L treatment for met NSCLC
		Oct 2015	met squamous NSCLC
		22 May 2015	unresectable or met melanoma
	TGA	15 Apr 2015	unresectable or met melanoma
		11 Jan 2018	2L treatment for unresectable or met UC 1L treatment for met NSCLC with PD-L1 ≥50% 2L treatment for met NSCLC with PD-L1 ≥1% 2L treatment for recurrent or met HNSCC r/r cHL
	PBS	1 Sep 2015	unresectable or met melanoma
Talimogene laherparepvec (T-vec)	USFDA	27 Oct 2015	met melanoma
	EMA	23 Oct 2015	met melanoma
	TGA	21 Dec 2015	unresectable melanoma
Axicabtagene ciloleucel	USFDA	18 Oct 2017	r/r adult large B-cell lymphoma
Tisagenlecleucel-T	USFDA	18 Oct 2017	r/r B-ALL

1L: first line; 2L: second line; B-ALL: B-cell acute lymphoblastic leukemia; cHL: classical Hodgkin lymphoma; CRC: colorectal cancer; cCRT: concurrent chemoradiotherapy; dMMR: DNA mismatch repair deficiency; EMA: European Medicines Agency; GEJ: gastroesophageal junction; HNSCC: head and neck squamous cell carcinoma; HCC: hepatocellular carcinoma; LA: locally advanced; met: metastatic; MSI-H: microsatellite instability-high; NSCLC: non-small cell lung cancer; PBS: Pharmaceutical Benefits Scheme; RCC: renal cell carcinoma; r/r: relapsed or refractory; TGA: Therapeutic Goods Administration; USFDA: United States Food and Drug Administration; UC: urothelial cancer;

Figure 1: *Cancer Immunity Cycle. Shown are afferent (stations 1-3) and efferent (stations 4-7) limbs of the cancer immune response. Afferent limb function depends on antigen presenting cells (APCs) and, critically, dendritic cells (DCs), to cross-prime antigen (Ag)-inexperienced T cells. Efferent limb function depends on full activation and infiltration of tumour-antigen specific killer CD8⁺ cytotoxic T lymphocytes (CTLs) via endothelial cells (ECs) [After Chen & Mellman 2013].*[38]

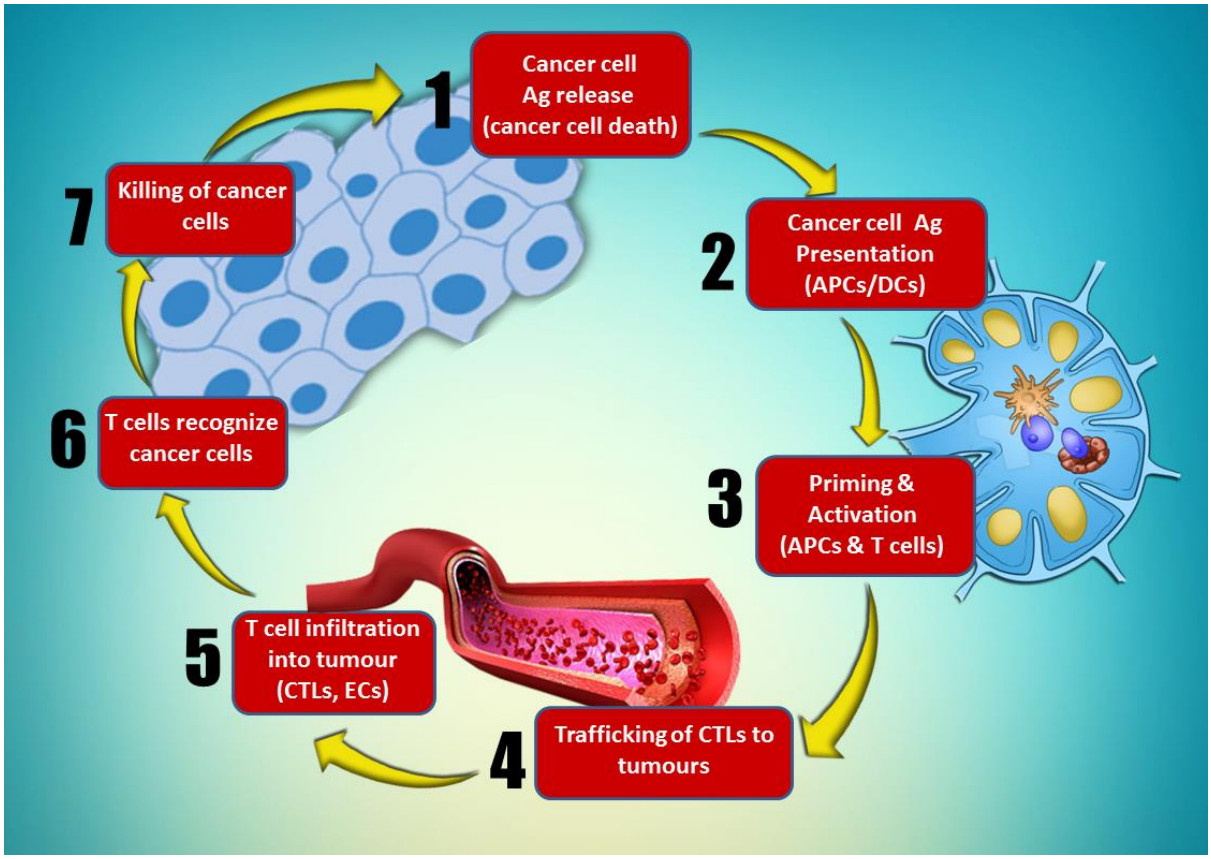


Figure 2: *Schematic Representation of T-cell Activation and Checkpoint Control. Signal 0: DC priming. Signal 1: Antigen (Ag) recognition and T-cell activation. Ag is processed as a short peptide bound in the cleft of a MHC molecule. Signal 2: Co-stimulation and T-cell survival. Signal 3: T-cell differentiation. Engagement of CTLA4 with B7 molecules, and of PDL1 with PD1, inhibits T-cell activation. Immune checkpoint inhibitors, i.e. anti-CTLA4 or anti-PD1/anti-PDL1 result in priming of new T cells or re-invigoration of exhausted T cells, respectively. CD: cluster of differentiation; CTLA4: cytotoxic T lymphocyte-associated molecule-4; DAMPs: damage-associated molecular patterns; DCs: dendritic cells; IFN: interferon; IL: interleukin; MHC: major histocompatibility complex; PAMPs: pathogen-associated molecular patterns; PD1: programmed cell death protein-1; PDL1: programmed cell death ligand-1; TCR: T-cell receptor.*

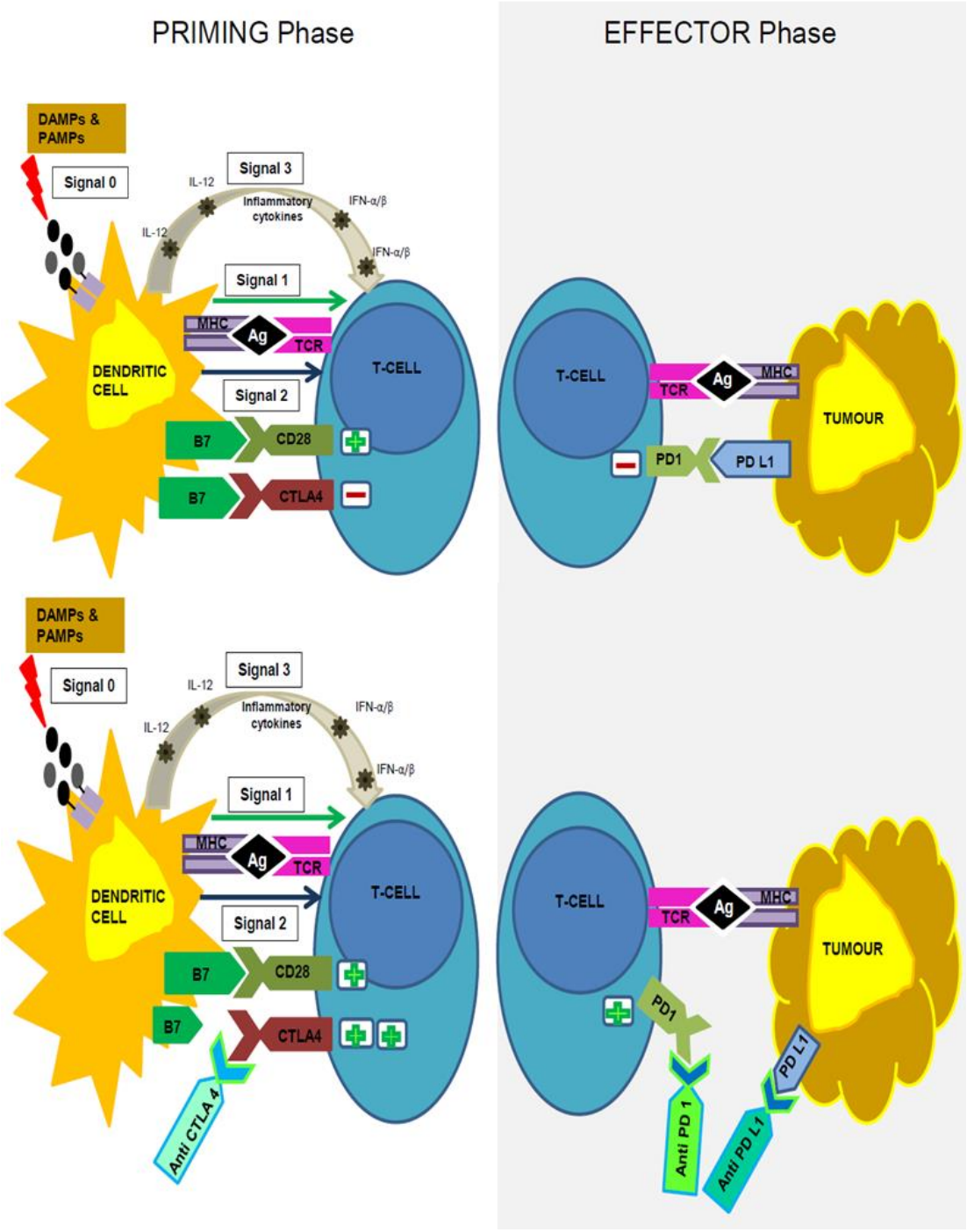


Figure 3: *Immune Checkpoint Inhibitor-Related Toxicities. Immune checkpoint inhibitors have a wide spectrum of organ-related toxicities. DRESS: drug rash with eosinophilia and systemic symptoms [adapted from Champiat et al].*[14]

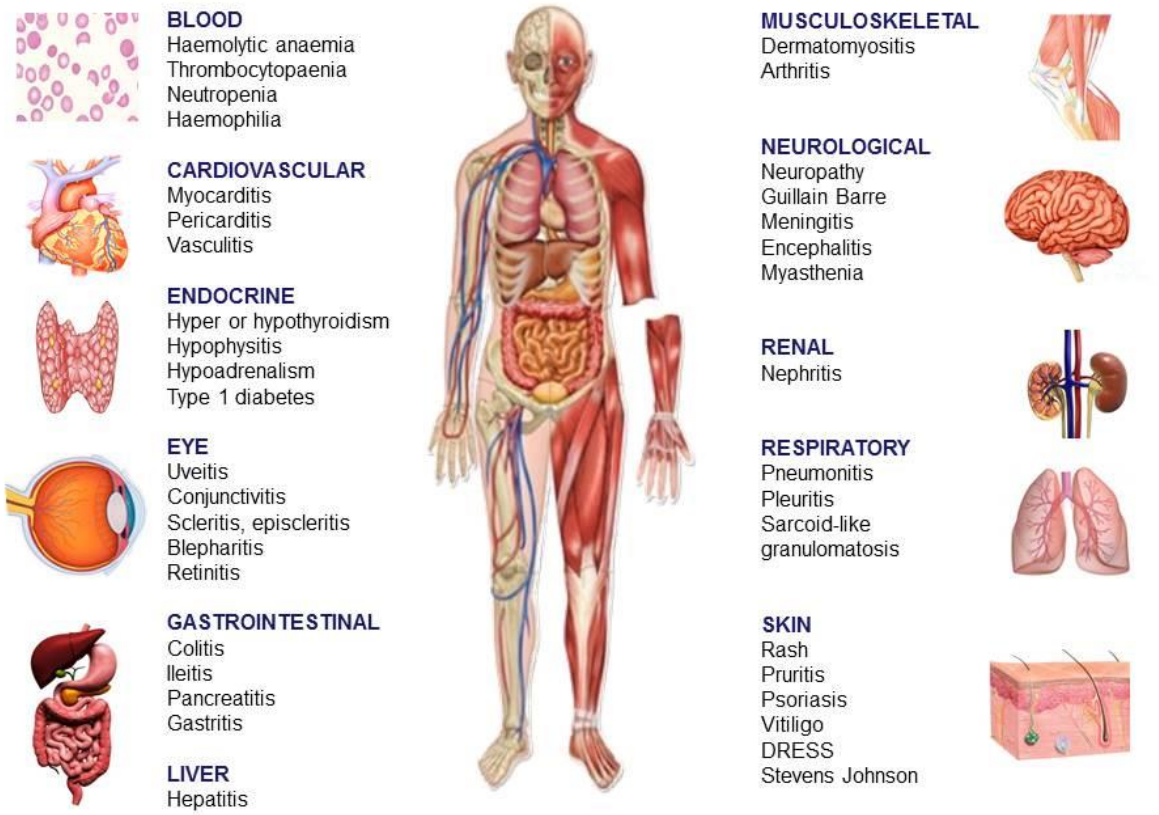
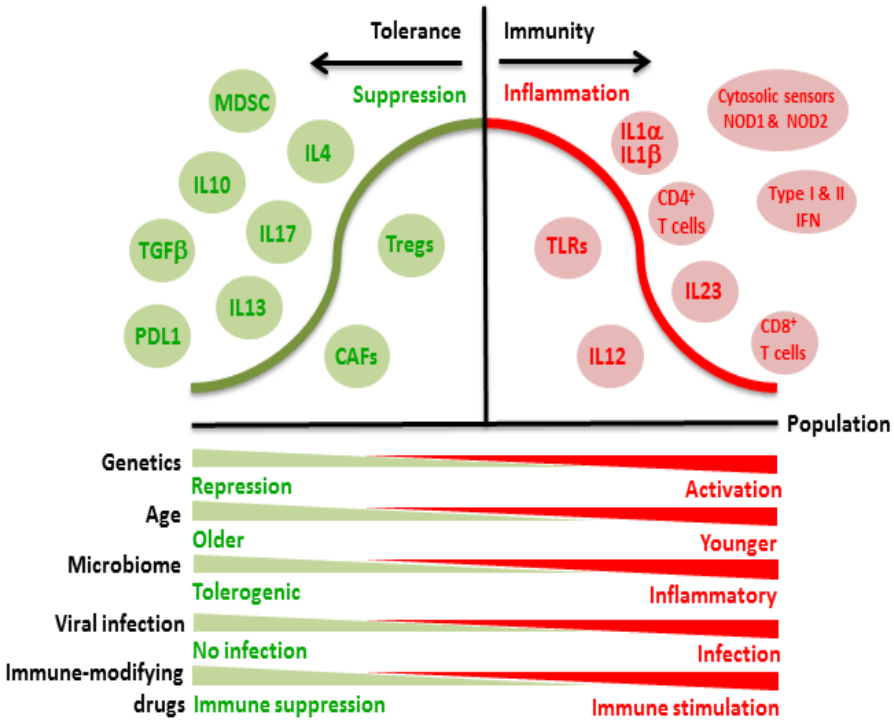


Figure 4: *Cancer-Immune Setpoint. Many parameters can influence human anti-cancer immunity including genetics, age, microbiome, viral infection, and immune-modifying drugs. An individualised setpoint is determined directly or indirectly by various tolerogenic (green) or immunogenic (red) cytokines, chemokines, and immune and other cell types. CAF: cancer associated fibroblast; IL: interleukin; IFN: interferon; MDSC: myeloid derived suppressor cell; NOD: nucleotide-binding oligomerization domain-like receptors; PDL1: programmed cell death ligand-1; TGFβ: transforming growth factor β; Tregs: regulatory T cells; TLRs: toll-like receptors [adapted from Chen and Mellman].*[39]



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