Imunoterapias

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Imunoterapia: conceito

Imunoterapia: uso de "componentes" do sistema imune (tais como células, anticorpos monoclonais, citocinas recombinantes), como ferramentas terapêuticas para o tratamento de doenças.

Imunoterapia: classificação

- Imunoterapia "ativadora": tratamento de doenças pela indução da resposta immune
- Imunoterapia "supressora": tratamento de doenças pela supressão da resposta immune

De acordo com as substâncias utilizadas e os seus mecanismos de ação, pode ser classificada em imunoterapia ativa ou passiva

Imunoterapia ativa

Imunoterapia ativa: substâncias estimulantes da função imunológica (imunoterapia inespecífica) e as vacinas "celulares" (imunoterapia específica) são administradas com a finalidade de estimular/intensificar a resposta imune.

- Imunoterapia inespecífica: BCG e derivados; levamisole; *Corynebacterium parvum*; citocinas recombinantes (tais como interferons e IL-2).
- Imunoterapia específica: vacinas "celulares" com Ags tumorais ou virais; vacinas celulares gênicas (ex. DCs ou MSCs transduzidas com IL-12). Vacinação convencional para doenças infecciosas.

Imunoterapia passiva ou adotiva

Imunoterapia passiva (ou adotiva): imunobiológicos /imunoterapêuticos (substâncias solúveis: anticorpos monoclonais, receptores solúveis, antagonistas de receptores, Igs totais purificadas) ou células exógenas são administrados, objetivando estimular/intensificar a capacidade imunológica de combate imediato à doença.

- Imunoterapia "humoral": imunobiológicos/imunoterapêuticos (substâncias solúveis tais como proteínas recombinantes, anticorpos monoclonais, Igs totais purificadas, soros)
- Imunoterapia celular: as células são transferidas para o paciente (transferência adotiva); células modificadas geneticamente ou "engenheiradas" (ex, CTHs transduzidas com gene ADA)

Outros conceitos/definições

- "Immunotherapeutics" (imunobiológicos, imunoterapêuticos): immunotherapeutic agents use or modify immune mechanisms. Different classes of immunotherapeutic agents have been developed:

  - Monoclonal antibodies
  - Fusion proteins
  - Soluble cytokine receptors
  - Recombinant cytokines
  - Small-molecule mimetics

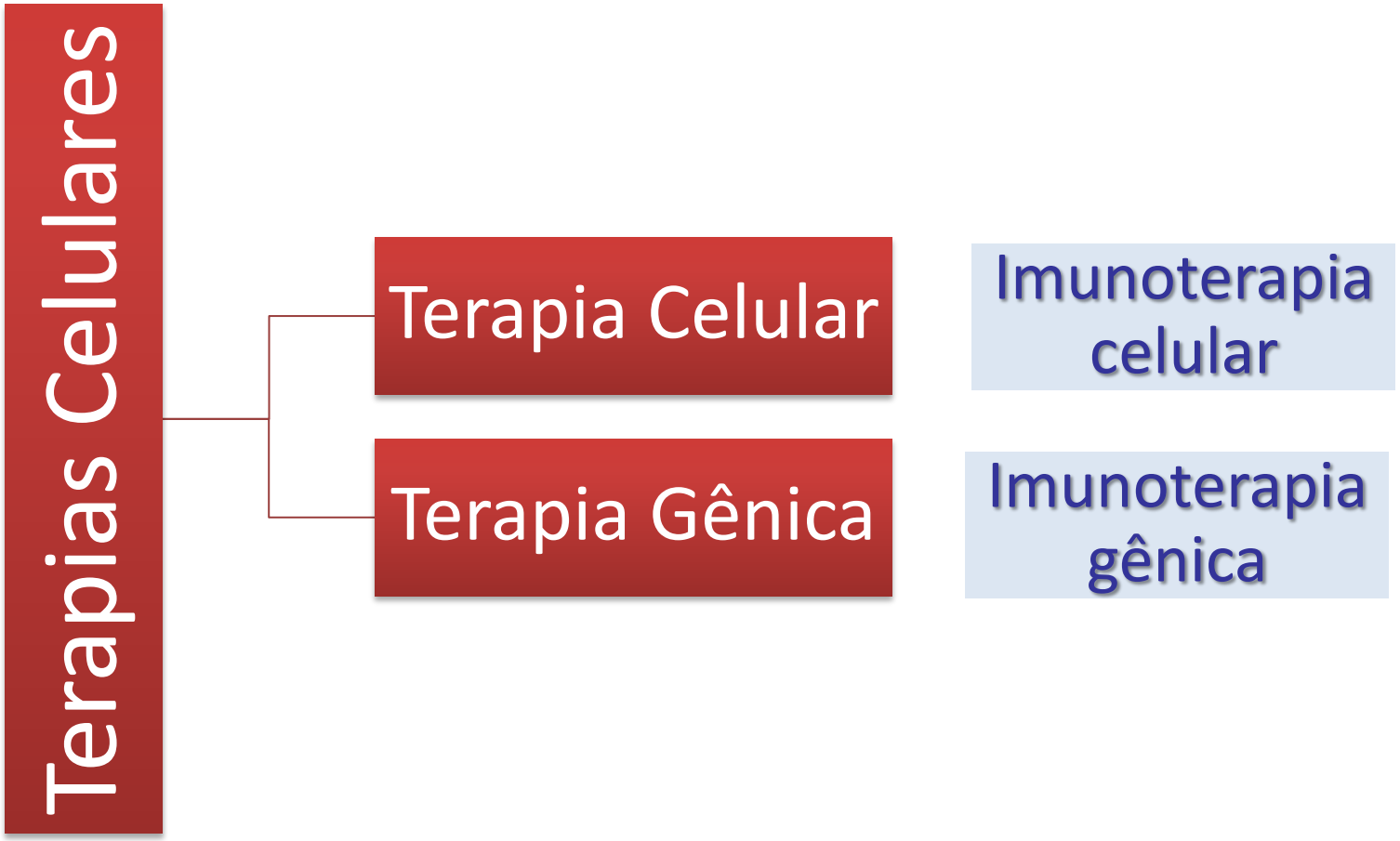
- "Biopharmaceuticals" (biofármacos): a pharmaceutical inherently biological in nature and manufactured using biotechnology. Examples:

  - Monoclonal antibodies
  - Recombinant cytokines

http://www.merckmanuals.com/

Terapia Celular: classificação

British Standard Institute definition of “cell-based therapy”: therapy in which cells are administered to the body to the benefit of the recipient



American Society of Gene & Cell Therapy; http://www.asgct.org/

Tipos de células usadas em Terapia Celular e Gênica

Células-Tronco

- Células-tronco pluripotentes (embrionárias e iPS)
- Células-tronco multipotentes (hematopoéticas; células estromais mesenquimais)

Células do sistema imune

- Células T (totais, TILs, CAR-T)
- Células NK
- Células dendríticas
- Células T reguladoras

"Imunoterapia celular"

Outras células

- Endoteliais
- Fibroblastos
- Ilhotas pancreáticas
- Células tecido-específicas

American Society of Gene & Cell Therapy; http://www.asgct.org/

Terapia Celular: histórico

- Transfusão sanguínea: primeiro tipo de terapia celular (rotina; hemoterapia)

- Transplante de medula óssea / Transplante de células-tronco hematopoéticas (1968): protocol complexo e bem estabelecido; terapia celular obteve legitimidade científica; procedimento clínico de rotina

Figure 1 | **Nobel prize for stem-cell transplantation.** Photograph of the Seattle team after announcement of the Nobel Prize in Medicine, which was awarded to E. D. Thomas in 1990. From left to right: Paul Neiman, Alexander Fefer, E. Donnall Thomas, C. Dean Buckner and Rainer Storb.

American Society of Gene & Cell Therapy; http://www.asgct.org/

Terapia Celular: cenário atual

"...cell therapy is the fourth and final therapeutic pillar of global healthcare."

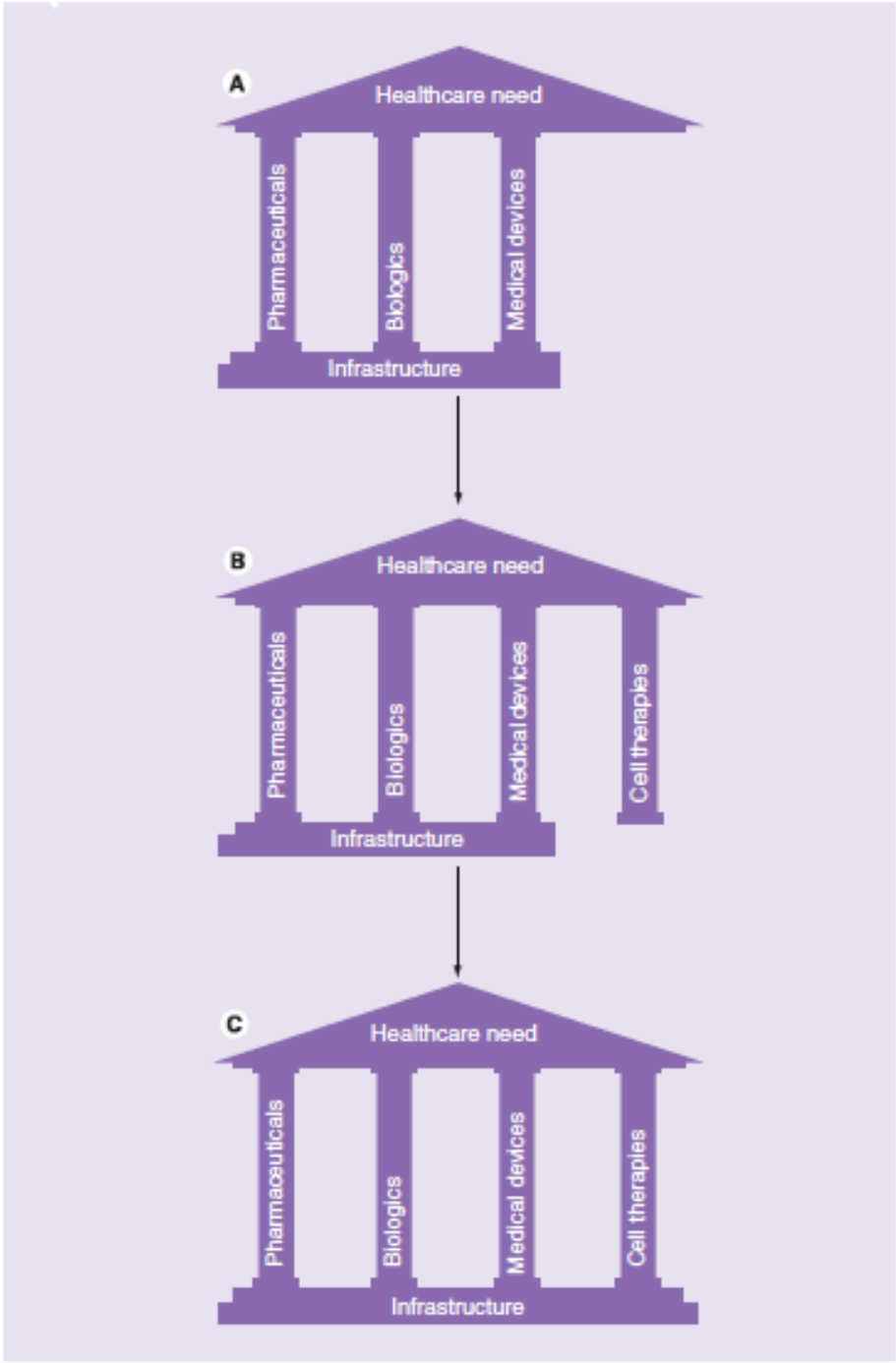
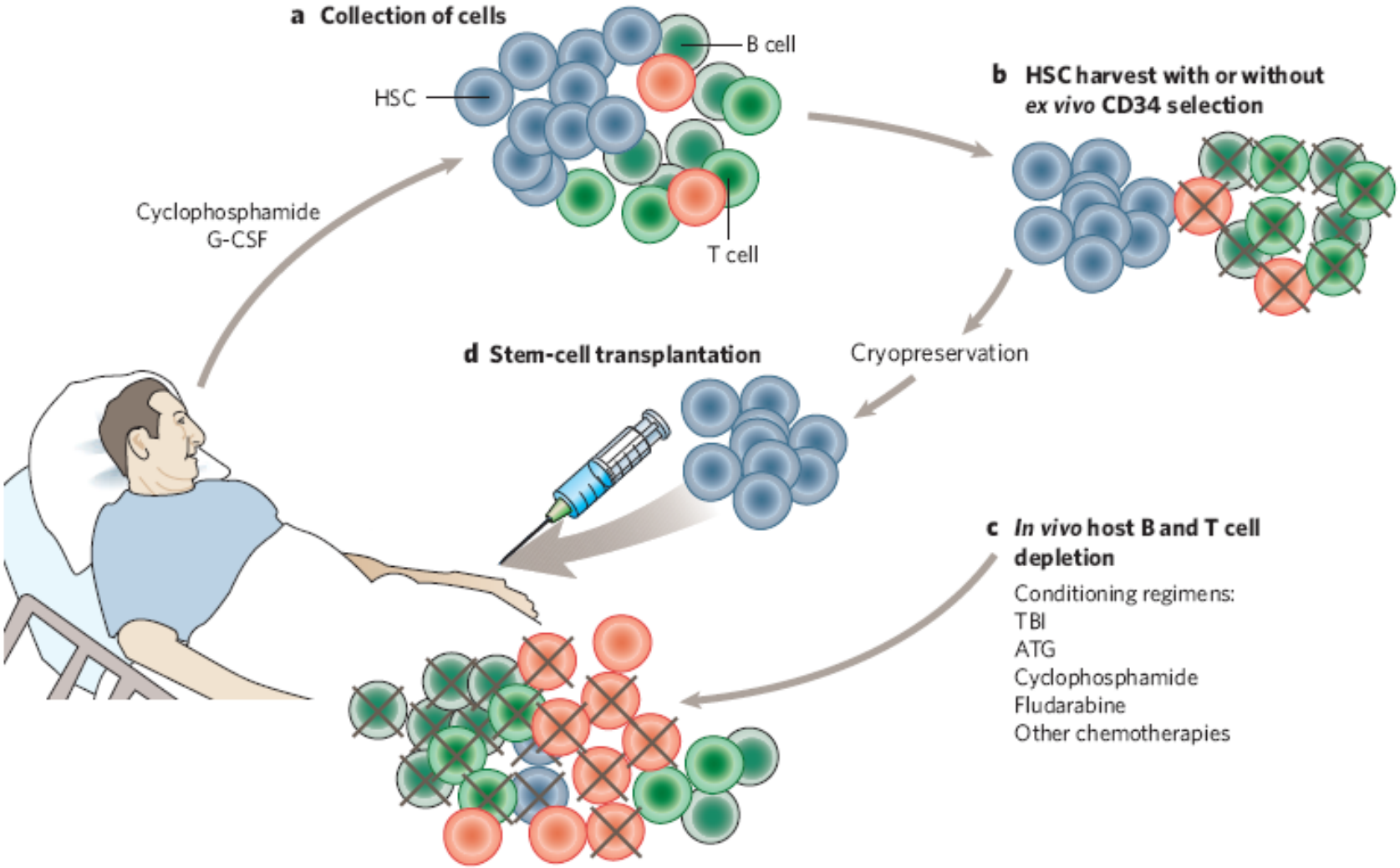


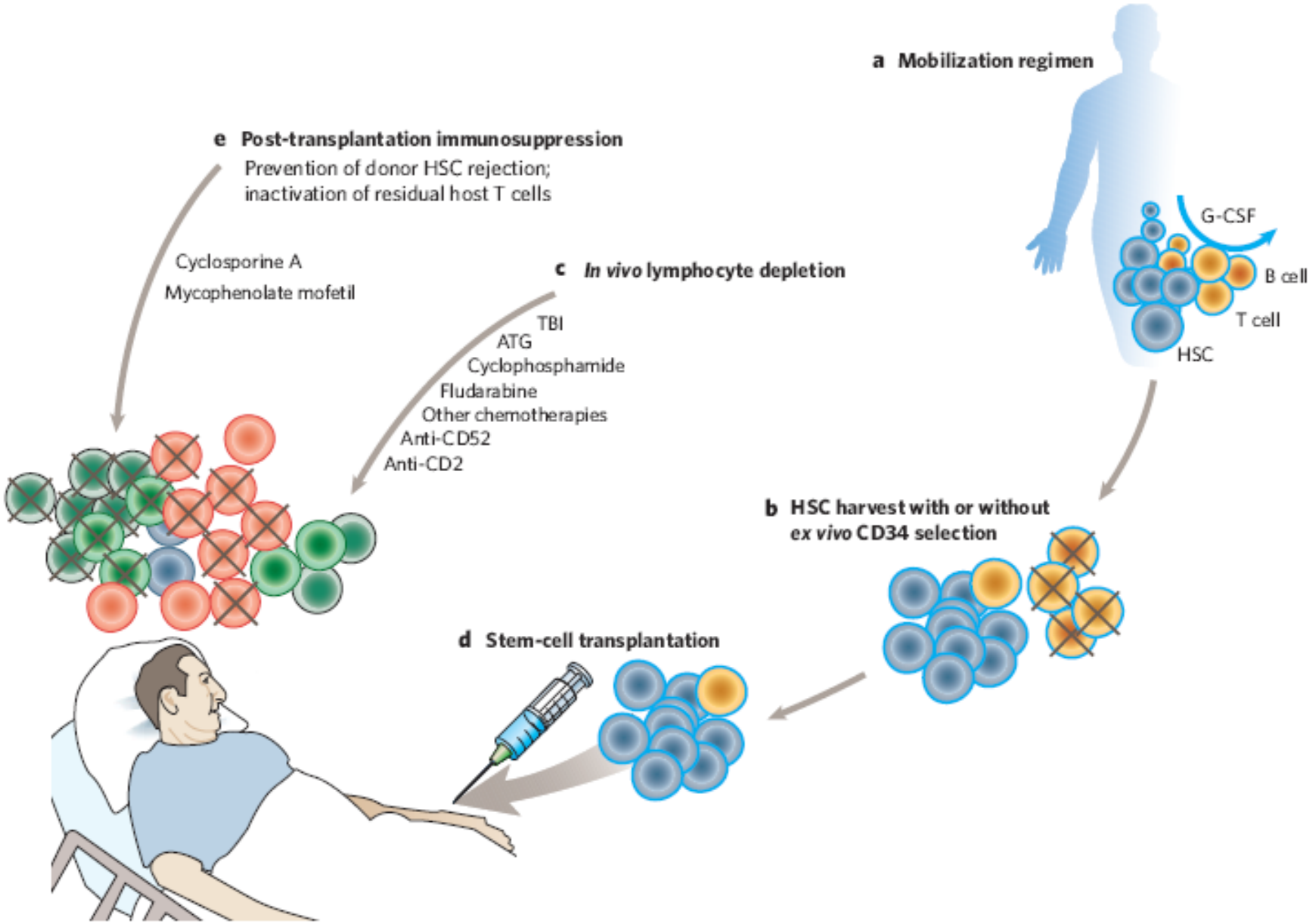
Figure 2. Cell therapy: the fourth and final therapeutic pillar of healthcare.

Regen. Med. (2011) **6**(3), 265–272

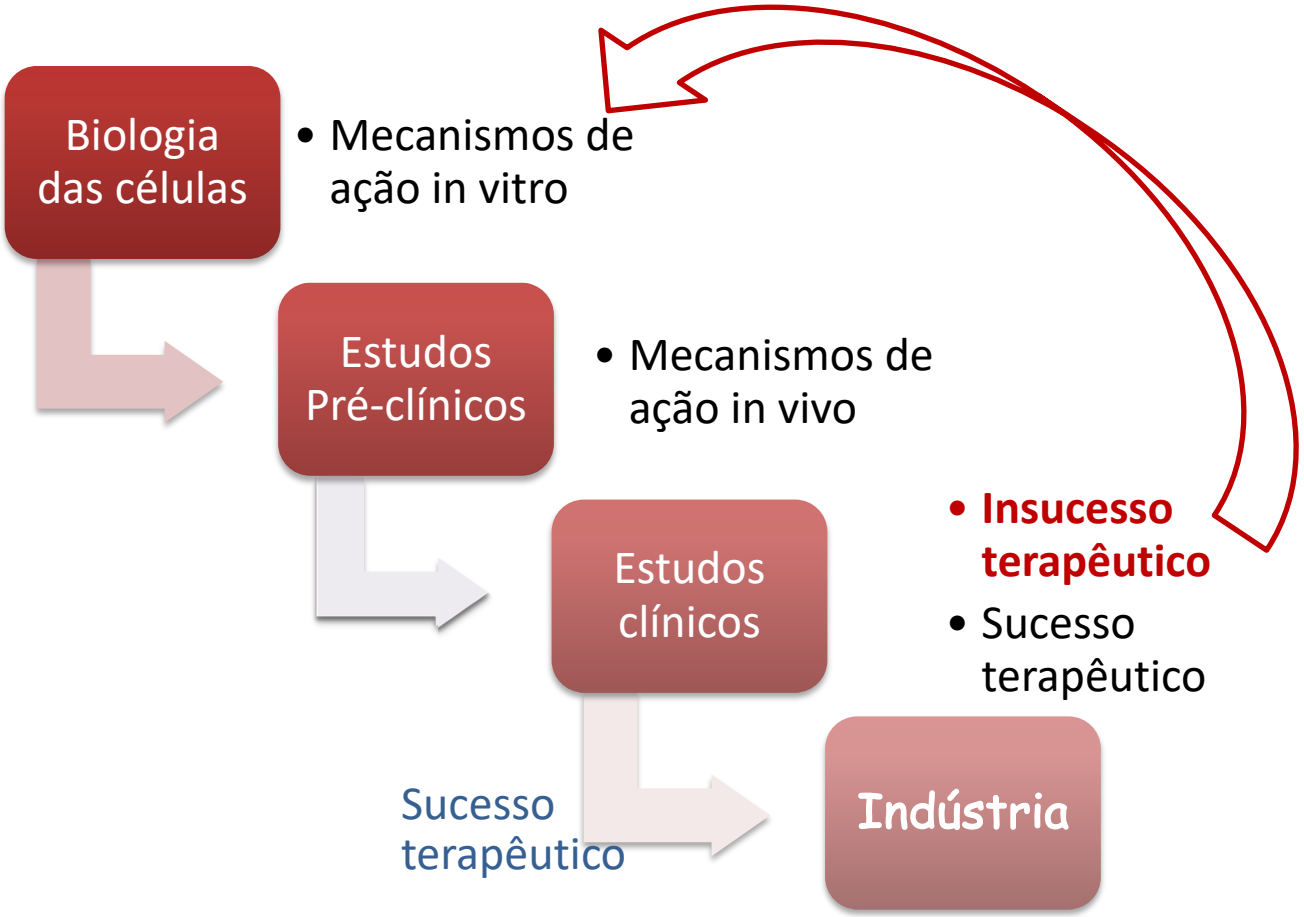
Terapia Celular: TCTH autólogo



Terapia Celular: TCTH alogênico



Terapia Celular: avanços importantes nas últimas 3 décadas

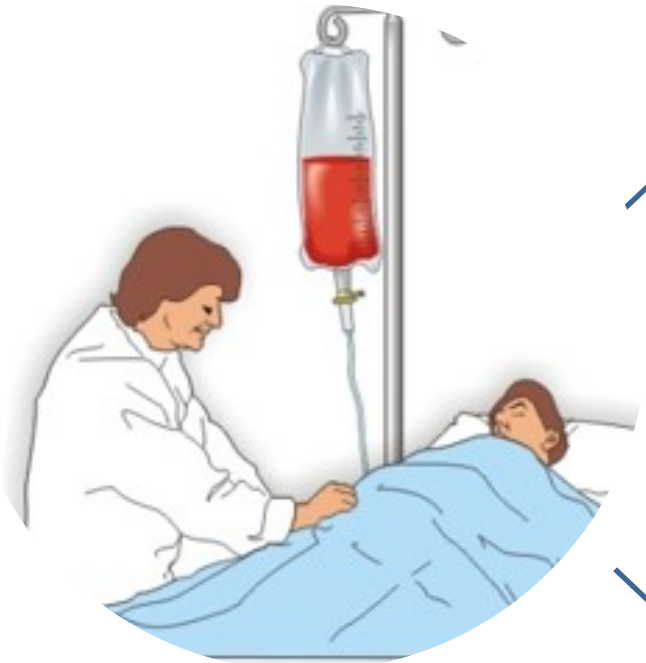


Cell Therapy Manucfacturing

American Society of Gene & Cell Therapy; http://www.asgct.org/

Terapia Celular: cenário atual

The translation of cell-based therapies: clinical landscape and manufacturing challenges



1342 active cell-based therapy clinical trials identified and characterized

Cell Type

Target indication

Trial phase

Regen. Med. (2015) 10(1), 49–64

Terapia Celular: cenário atual

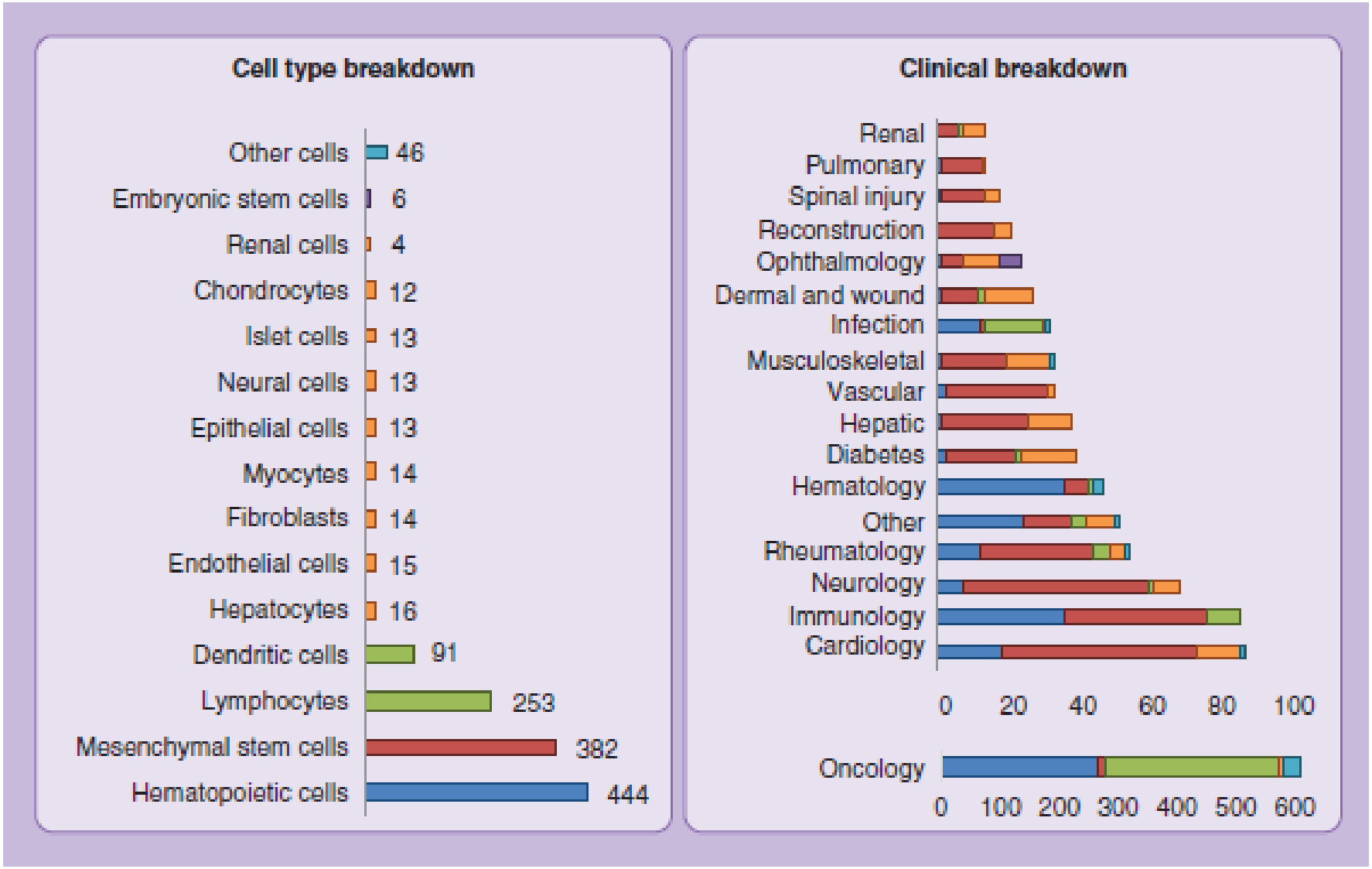
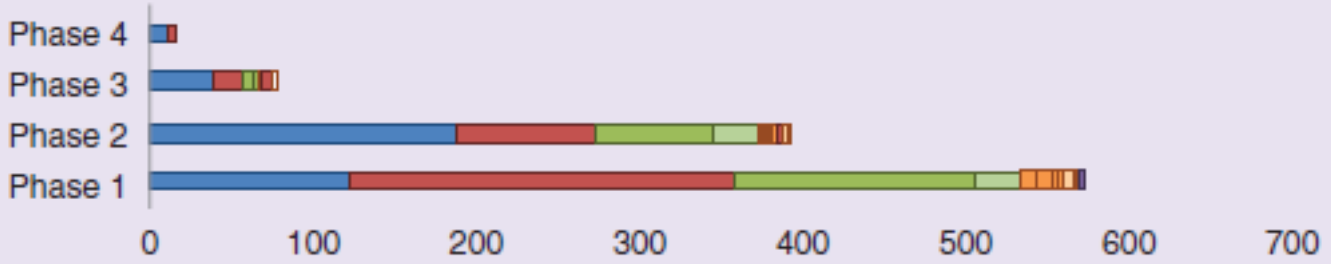


Figure 1. Number of active clinical trials by cell type and target clinical indication. Displaying broader cell type categories of hematopoietic (blue), mesenchymal stem cells (red), immune cells (green), tissue-specific cells (orange), embryonic stem cells (purple) and other (aqua).

Regen. Med. (2015) 10(1), 49–64

Terapia Celular: cenário atual



	Phase 1	Phase 2	Phase 3	Phase 4
Hematopoietic cells	118	187	39	10
Mesenchymal stem cells	232	88	19	0
Lymphocytes	146	72	7	2
Dendritic cells	43	30	3	0
Hepatocytes	9	3	0	0
Endothelial cells	9	3	0	0
Fibroblasts	3	3	3	2
Myocytes	5	4	2	0
Epithelial cells	2	2	2	1
Neural cells	10	2	0	0
Islet cells	3	6	2	0
Chondrocytes	2	3	4	0
Renal cells	1	0	0	1
Embryonic stem cells	6	0	0	0

Regen. Med. (2015) 10(1), 49–64

Figure 5. Breakdown of current active cell therapy clinical trials by cell group and trial phase.

Immunotherapy – Breakthrough 2013

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Breakthrough of the Year 2013

Immunotherapy – Breakthrough 2013

Cancer Immunoth

This year marks a turning point in cancer, as long-sought efforts t
system against tumors are paying off—even if the future rema

History's path is unchartable when it's not yet past but present, when we are still standing in the middle of it. That's what made *Science*'s selection of this year's Breakthrough of the Year such a topic of internal debate, even anxiety. In celebrating cancer immunotherapy—harnessing the immune system to battle tumors—did we risk hyping an approach whose ultimate impact remains unknown? Were we irresponsible to label as a breakthrough a strategy that has touched a tiny fraction of cancer patients and helped only some of them? What do we mean when we call something a breakthrough, anyway?

Ultimately, we concluded, cancer immunotherapy passes the test. It does so because this year, clinical trials have cemented its potential in patients and swayed even the skeptics. The field hums with stories of lives extended: the woman with a grapefruit-size tumor in her lung from melanoma, alive and healthy 13 years later; the 6-year-old near death from leukemia, now in third grade and in remission; the man with metastatic kidney cancer whose disease continued fading away even after treatment stopped.

As the anecdotes coalesce into data, there's another layer, too, a sense of paradigms shifting. Immunotherapy marks an entirely different way of treating cancer—by targeting the immune system, not the tumor itself. Oncologists,

a grounded-in-reality bunch, and we won't be going back.

With much pressure these insights into lifesaving drugs from immunotherapy's succ careful decoding of basic years. The early steps were t James Allison, now at th Anderson Cancer Center in Houston. In the late 1980s, French researchers who weren't thinking about cancer at all identified a new protein receptor on the surface of T cells, called cytotoxic T-lymphocyte antigen 4, or CTLA-4. Allison found that CTLA-4 puts the brakes on T cells, preventing them from launching full-out immune attacks. He wondered whether bloc blocker—the CTLA-4 mol would set the immune syster destroy cancer.

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Seek and destroy. Instead o Immunotherapy enlists the i an antibody (pink) blocks (gray), setting off a chain cancer cells (brown).

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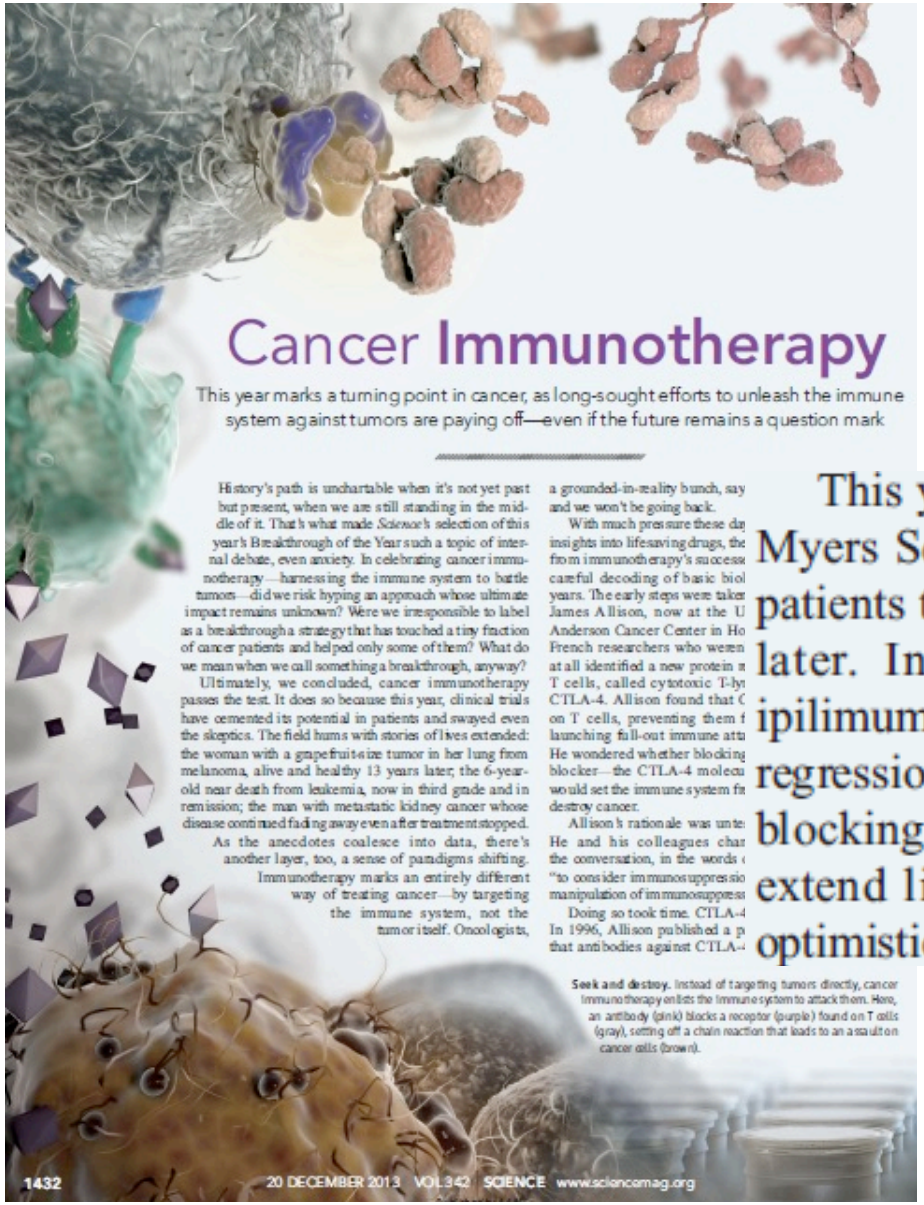
Online

away. At a meeting in New Orleans this month, June's team and another at Memorial Sloan-Kettering Cancer Center in New York reported that the T cell therapy in their studies put 45 of 75 adults and children with leukemia into complete remission, although some later relapsed. CAR therapy is now the focus of numerous clinical trials. Researchers hope that it, like the antibodies, can target an assortment of cancers.

Immunotherapy – Breakthrough 2013



Cancer Immunotherapy

This year marks a turning point in cancer, as long-sought efforts to unleash the immune system against tumors are paying off—even if the future remains a question mark

History's path is unchartable when it's not yet past but present, when we are still standing in the middle of it. That's what made *Science*'s selection of this year's Breakthrough of the Year such a topic of internal debate, even anxiety. In celebrating cancer immunotherapy—harnessing the immune system to battle tumors—did we risk hyping an approach whose ultimate impact remains unknown? Were we irresponsible to label as a breakthrough a strategy that has touched a tiny fraction of cancer patients and helped only some of them? What do we mean when we call something a breakthrough, anyway?

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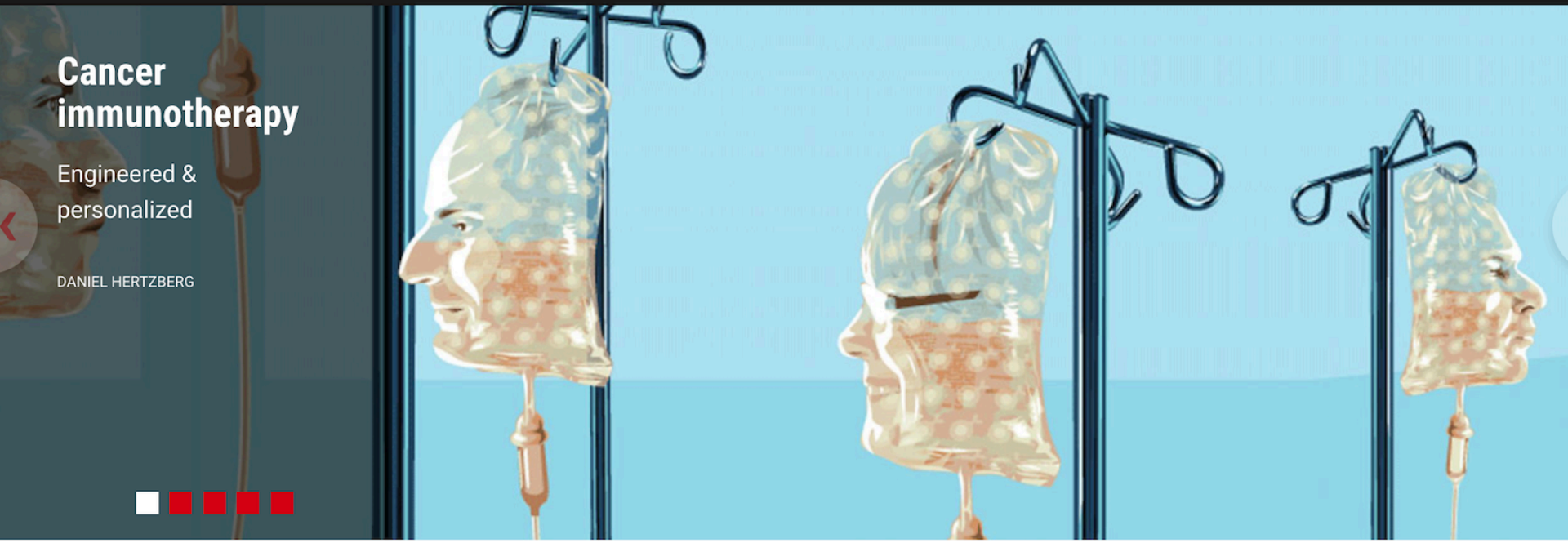
Seek and destroy. Instead of targeting tumors directly, cancer immunotherapy enlists the immune system to attack them. Here, an antibody (pink) blocks a receptor (purple) found on T cells (gray), setting off a chain reaction that leads to an assault on cancer cells (brown).

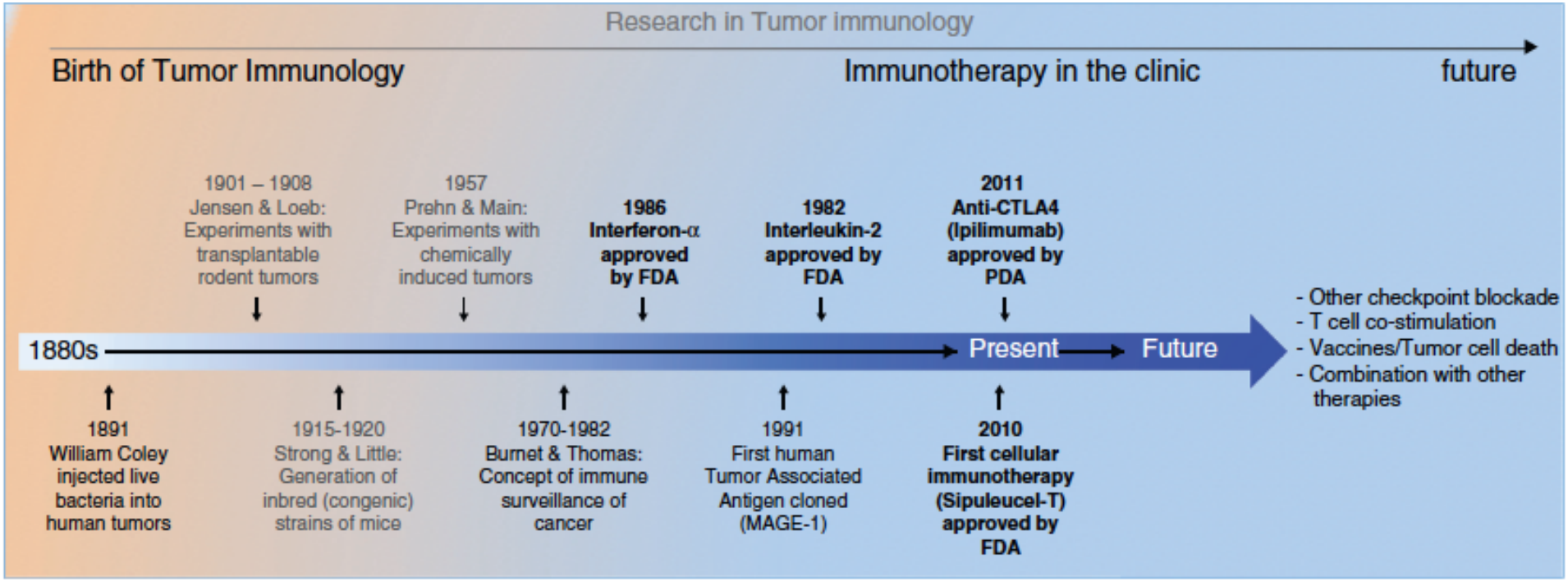
This year brought even more encouragement. Bristol-Myers Squibb reported this fall that of 1800 melanoma patients treated with ipilimumab, 22% were alive 3 years later. In June, researchers reported that combining ipilimumab and anti–PD-1 led to "deep and rapid tumor regression" in almost a third of melanoma patients. Drugs blocking the PD-1 pathway have not yet been proven to extend life, although survival rates so far have doctors optimistic that they do.

Immunotherapy 2013-2018

Immunotherapy 2018



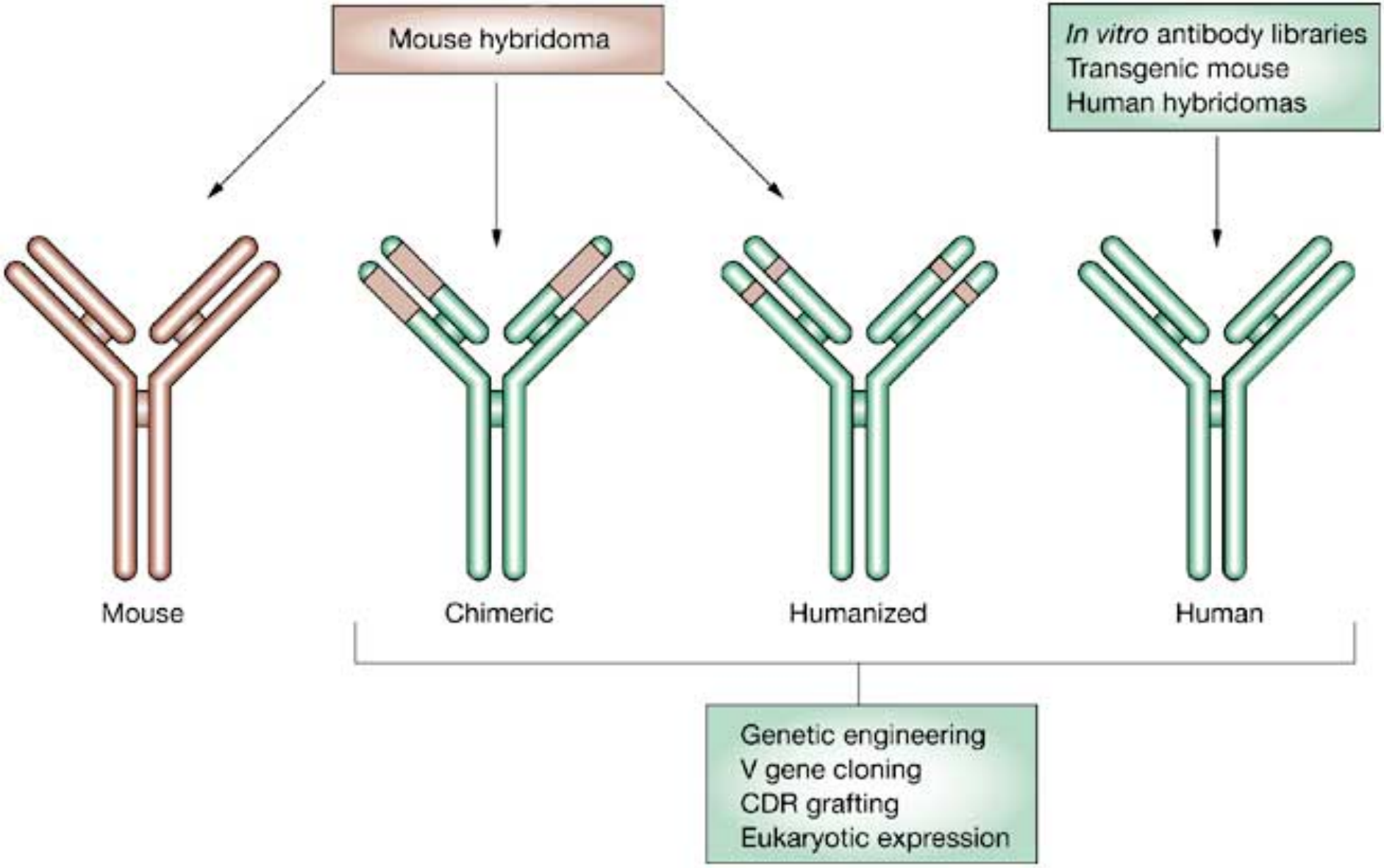
Imunoterapia em câncer: histórico



Current Opinion in Genetics & Development

Imunoterapia com anticorpos monoclonais

Anticorpos monoclonais em uso clínico



Strand V et al., Nature Review Drug Discovery, 2007

Nomenclatura anticorpos monoclonais

Complete list of stems for monoclonal antibody nomenclature[1]

Prefix	Target		Source		Suffix
variable	*-vi(r)-*	viral	*-u-*	human	*-mab*
	-ba(c)-	bacterial	*-o-*	mouse	
	-li(m)-	immune system	*-a-*	rat	
	-le(s)-	infectious lesions	*-e-*	hamster	
	-ci(r)-	cardiovascular	*-i-*	primate	
	-fu(ng)-	fungal	*-xi-*	chimeric	
	-ne(r)-	nervous system	*-zu-*	humanized	
	-ki(n)-	interleukin as target	*-axo-*	rat/murine hybrid	
	-mu(l)-	musculoskeletal	*-xizu-*	chimeric + humanized	
	-o(s)-	bone			
	-tox(a)-	toxin as target			
	-co(l)-	colonic tumor			
	-me(l)-	melanoma			
	-ma(r)-	mammary tumor			
	-go(t)-	testicular tumor			
	-go(v)-	ovarian tumor			
	-pr(o)-	prostate tumor			
	-tu(m)-	miscellaneous tumor			

Adalimumab is a drug targeting TNF alpha. When broken down into ***ada***- + -***lim***- + -***u***- + -***mab***, this compound is a human monoclonal antibody, of human source, targeting the immune system.

Anticorpos monoclonais aprovados para uso clínico

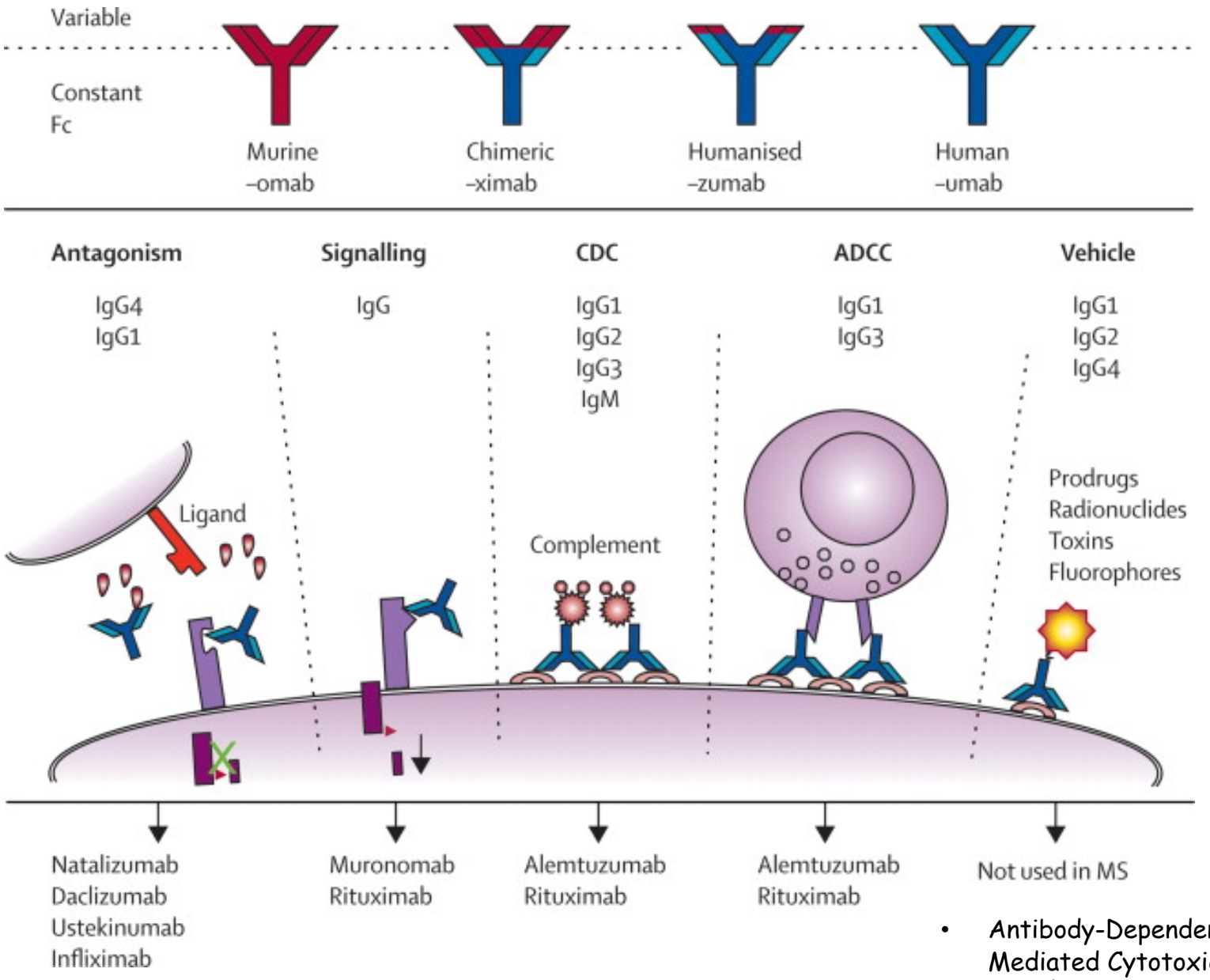
Example FDA approved therapeutic monoclonal antibodies[1]

Antibody	Brand name	Approval date	Type	Target	Approved treatment (s)
Abciximab	ReoPro	1994	chimeric	inhibition of glycoprotein IIb/IIIa	Cardiovascular disease
Adalimumab	Humira	2002	human	inhibition of TNF-α signaling	Several auto-immune disorders
Alemtuzumab	Campath	2001	humanized	CD52	Chronic lymphocytic leukemia
Basiliximab	Simulect	1998	chimeric	IL-2Rα receptor (CD25)	Transplant rejection
Bevacizumab	Avastin	2004	humanized	Vascular endothelial growth factor (VEGF)	Colorectal cancer
Cetuximab	Erbitux	2004	chimeric	epidermal growth factor receptor	Colorectal cancer, Head and neck cancer
Certolizumab pegol	Cimzia	2008	humanized	inhibition of TNF-α signaling	Crohn's disease
Daclizumab	Zenapax	1997	humanized	IL-2Rα receptor (CD25)	Transplant rejection

Anticorpos monoclonais aprovados para uso clínico

Efalizumab	Raptiva	2002	humanized	CD11a	Psoriasis
Gemtuzumab	Mylotarg	2000	humanized	CD33	Acute myelogenous leukemia (with calicheamicin)
Ibritumomab tiuxetan	Zevalin	2002	murine	CD20	Non-Hodgkin lymphoma (with yttrium-90 or indium-111)
Infliximab	Remicade	1998	chimeric	inhibition of TNF-α signaling	Several autoimmune disorders
Muromonab-CD3	Orthoclone OKT3	1986	murine	T cell CD3 Receptor	Transplant rejection
Natalizumab	Tysabri	2006	humanized	alpha-4 (α4) integrin,	Multiple sclerosis and Crohn's disease
Omalizumab	Xolair	2004	humanized	immunoglobulin E (IgE)	mainly allergy-related asthma
Palivizumab	Synagis	1998	humanized	an epitope of the RSV F protein	Respiratory Syncytial Virus
Panitumumab	Vectibix	2006	human	epidermal growth factor receptor	Colorectal cancer
Ranibizumab	Lucentis	2006	humanized	Vascular endothelial growth factor A (VEGF-A)	Macular degeneration
Rituximab	Rituxan, Mabthera	1997	chimeric	CD20	Non-Hodgkin lymphoma

Anticorpos monoclonais em uso clínico



- Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC)
- Complement Dependent Cytotoxicity (CDC).

Strand V et al., Nature Review Drug Discovery, 2007

"Tipos" de anticorpos – uso potencial em oncologia

Table 1 | **Antibody constructs and potential uses in oncology**

Antibody constructs	Examples of targets	Potential clinical use
scFv	CC49, ERBB2 and Le^y	Imaging and cell targeting
Diabody	Le^y and TAG-72	Imaging and drug delivery
Affibody	ERBB2	Imaging and drug delivery
Minibody	CEA and ERBB2	Imaging and drug delivery
Protein–Fc	Angiopoietin 1, angiopoietin 2, VEGFR1 and VEGFR2	Imaging and therapy
Intact IgG	CD20, CD33, EGFR, ERBB2 and VEGF	Imaging therapy and drug delivery
IgE and IgM	GM2	Therapy
Drug conjugates	CD30, CD33 and ERBB2	Therapy
Loaded nanoparticles	A33, EGFR and transferrin	Drug delivery
Bispecifics	CD19–CD3, EPCAM–CD3 and gp100–CD3	Therapy

CEA, carcinoembryonic antigen; EGFR, epidermal growth factor receptor; EPCAM, epithelial cell adhesion molecule; gp100, glycoprotein 100; Ig, immunoglobulin; Le^y, Lewis Y antigen; scFv, single-chain variable fragment; TAG-72, tumour-associated glycoprotein 72; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor.

Scott AM et al., Nature Review Cancer (Vol 12), 2012

Monoclonal antibodies currently FDA approved in oncology and their mechanisms of action

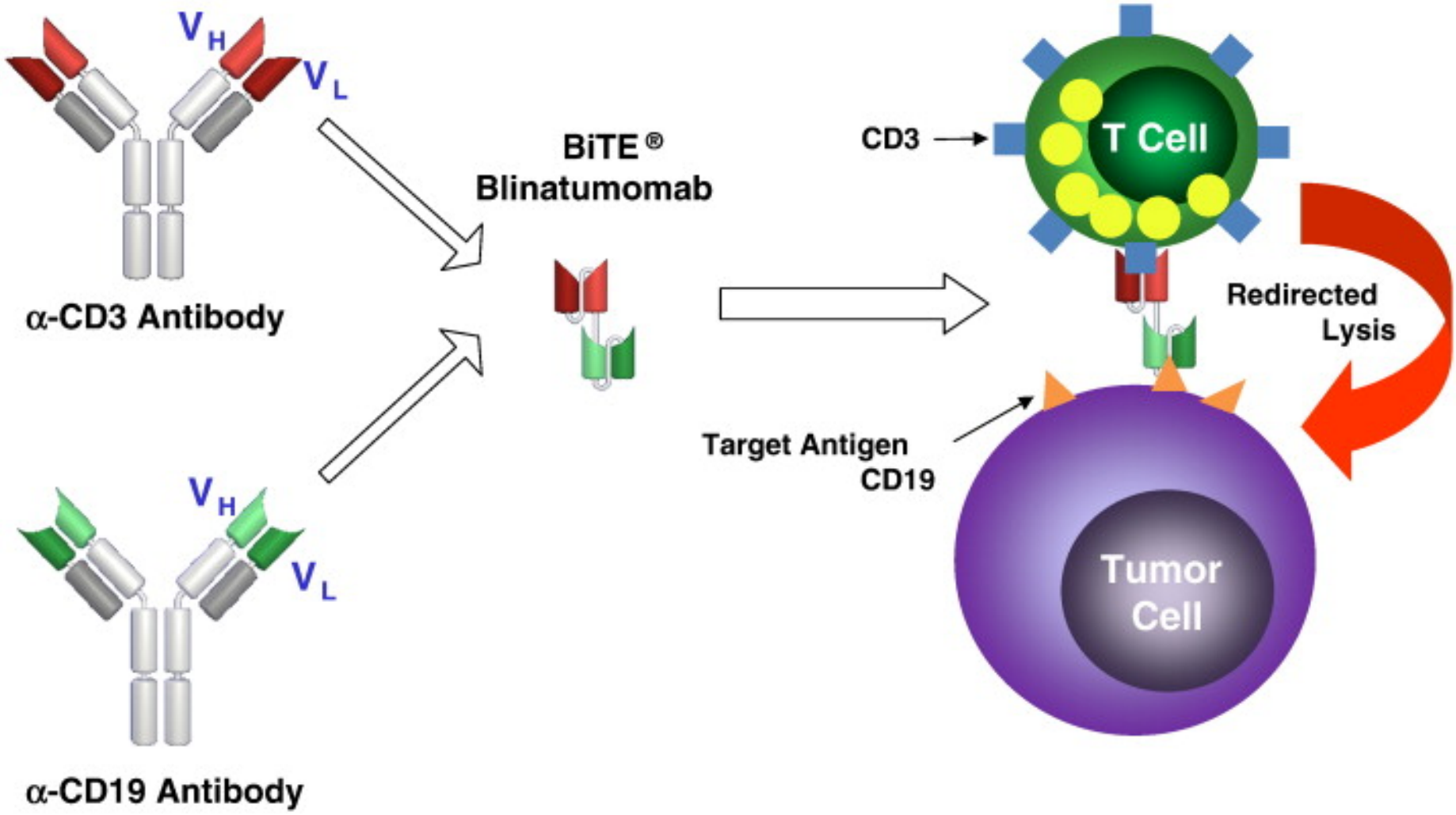
Antibody	Target	FDA-approved indication	Approval in Europe*	Mechanisms of action
Naked antibodies: solid malignancies				
Trastuzumab (Herceptin; Genentech): humanized IgG1	ERBB2	ERBB2-positive breast cancer, as a single agent or in combination with chemotherapy for adjuvant or palliative treatment	Similar	Inhibition of ERBB2 signalling and ADCC
		ERBB2-positive gastric or gastro-oesophageal junction carcinoma as first-line treatment in combination with cisplatin and capecitabine or 5-fluorouracil		
Bevacizumab (Avastin; Genentech/Roche): humanized IgG1	VEGF	For first-line and second-line treatment of metastatic colon cancer, in conjunction with 5-fluorouracil-based chemotherapy; for first-line treatment of advanced NSCLC, in combination with carboplatin and paclitaxel, in patients who have not yet received chemotherapy; as a single agent in adult patients with glioblastoma whose tumour has progressed after initial treatment; and in conjunction with IFNα to treat metastatic kidney cancer	Similar	Inhibition of VEGF signalling
Cetuximab (Erbitux; Bristol-Myers Squibb)‡: chimeric human–murine IgG1	EGFR	In combination with radiation therapy for the initial treatment of locally or regionally advanced SCCHN; as a single agent for patients with SCCHN for whom prior platinum-based therapy has failed; and palliative treatment of pretreated metastatic EGFR-positive colorectal cancer	Similar	Inhibition of EGFR signalling and ADCC
Panitumumab (Vectibix; Amgen)‡: human IgG2	EGFR	As a single agent for the treatment of pretreated EGFR-expressing, metastatic colorectal carcinoma	Similar	Inhibition of EGFR signalling
Ipilimumab (Yervoy; Bristol-Myers Squibb): IgG1	CTLA4	For the treatment of unresectable or metastatic melanoma	Similar	Inhibition of CTLA4 signalling
Naked antibodies: haematological malignancies				
Rituximab (Mabthera; Roche): chimeric human–murine IgG1	CD20	For the treatment of CD20-positive B cell NHL and CLL, and for maintenance therapy for untreated follicular CD20-positive NHL	Similar	ADCC, direct induction of apoptosis and CDC
Alemtuzumab (Campath; Genzyme): humanized IgG1	CD52	As a single agent for the treatment of B cell chronic lymphocytic leukaemia	Similar	Direct induction of apoptosis and CDC
Ofatumumab (Arzerra; Genmab): human IgG1	CD20	Treatment of patients with CLL refractory to fludarabine and alemtuzumab	Similar	ADCC and CDC
Conjugated antibodies: haematological malignancies				
Gemtuzumab ozogamicin (Mylotarg; Wyeth): humanized IgG4	CD33	For the treatment of patients with CD33-positive acute myeloid leukaemia in first relapse who are 60 years of age or older and who are not considered candidates for other cytotoxic chemotherapy; withdrawn from use in June 2010	Not approved in the European Union	Delivery of toxic payload, calicheamicin toxin
Brentuximab vedotin (Adcetris; Seattle Genetics): chimeric IgG1	CD30	For the treatment of relapsed or refractory Hodgkin's lymphoma and systemic anaplastic lymphoma	Not approved in the European Union	Delivery of toxic payload, auristatin toxin
^{90}Y-labelled ibritumomab tiuxetan (Zevalin; IDEC Pharmaceuticals): murine IgG1	CD20	Treatment of relapsed or refractory, low-grade or follicular B cell NHL	Similar	Delivery of the radioisotope ^{90}Y
		Previously untreated follicular NHL in patients who achieve a partial or complete response to first-line chemotherapy		
^{131}I-labelled tositumomab (Bexxar; GlaxoSmithKline): murine IgG2	CD20	Treatment of patients with CD20 antigen-expressing relapsed or refractory, low-grade, follicular or transformed NHL	Granted orphan status drug in 2003 in the European Union	Delivery of the radioisotope ^{131}I, ADCC and direct induction of apoptosis

ADCC, antibody-dependent cellular cytotoxicity; CDC, complement-dependent cytotoxicity; CLL, chronic lymphocytic leukaemia; CTLA4, cytotoxic T lymphocyte-associated antigen 4; EGFR, epidermal growth factor receptor; FDA, US Food and Drug Administration; IgG, immunoglobulin G; INFα; interferon-α; NHL, non-Hodgkin's lymphoma; NSCLC, non-small-cell lung cancer; SCCHN, squamous cell carcinoma of the head and neck; VEGF, vascular endothelial growth factor. *Based on information from the European Medicines Agency. ‡Not recommended for patients with colorectal cancer whose tumours express mutated KRAS.

Vanneman M and Dranoff G, Nature Review Cancer (Vol 12), 2012

Anticorpos bi-específicos

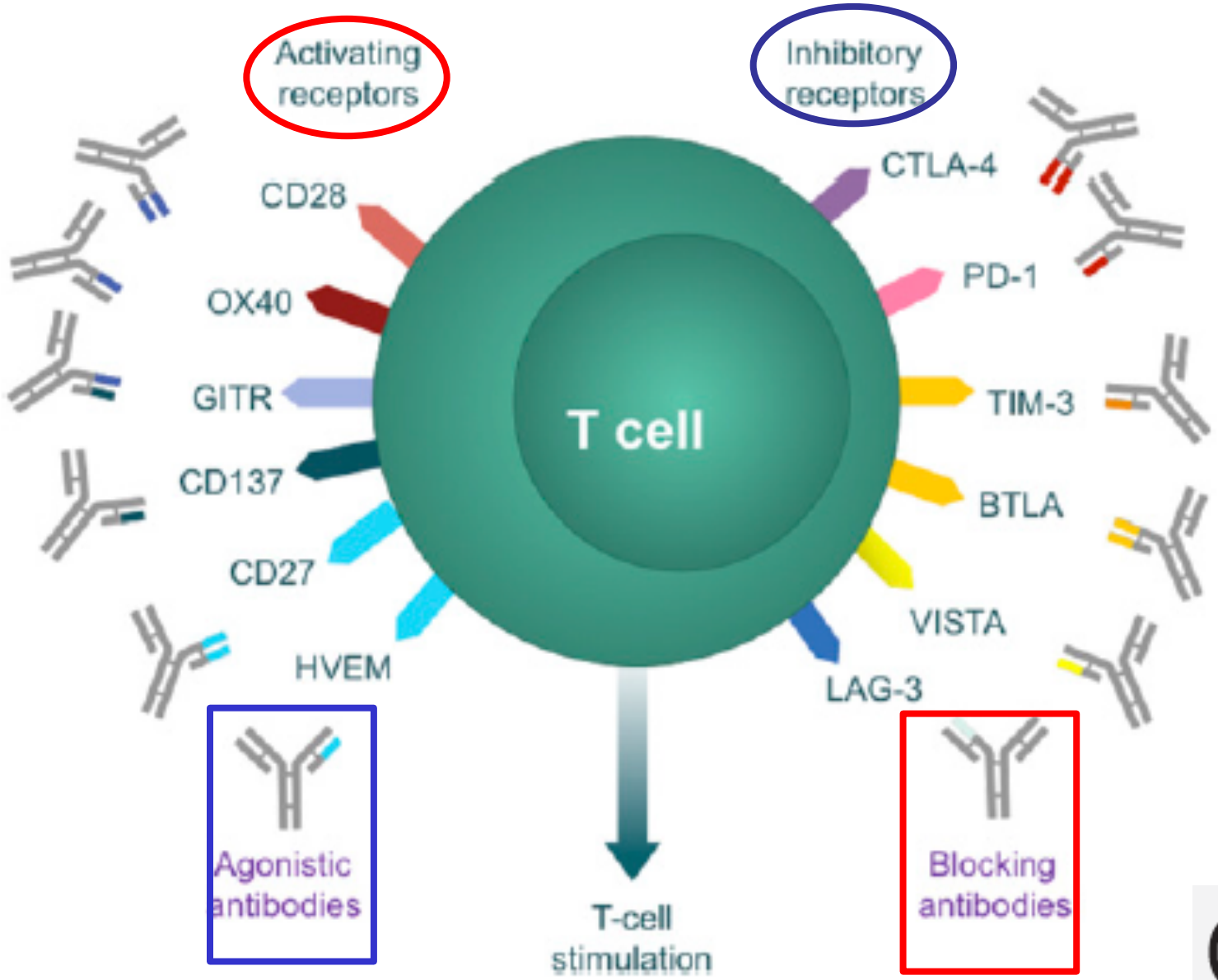
Ex: Blinatumumab



Topp M S et al. JCO 2011;29:2493-2498

The Evolving Role of Immune Checkpoint Inhibitors in Cancer Treatment

GREGORY K. PENNOCK,[a] LAURA Q.M. CHOW[b]



The Oncologist 2015;20:812–822

The Oncologist®

Haematological malignancies: at the forefront of immunotherapeutic innovation

Pavan Bachireddy[1–3], Ute E. Burkhardt[1], Mohini Rajasagi[1,2,4] and Catherine J. Wu[1–3]

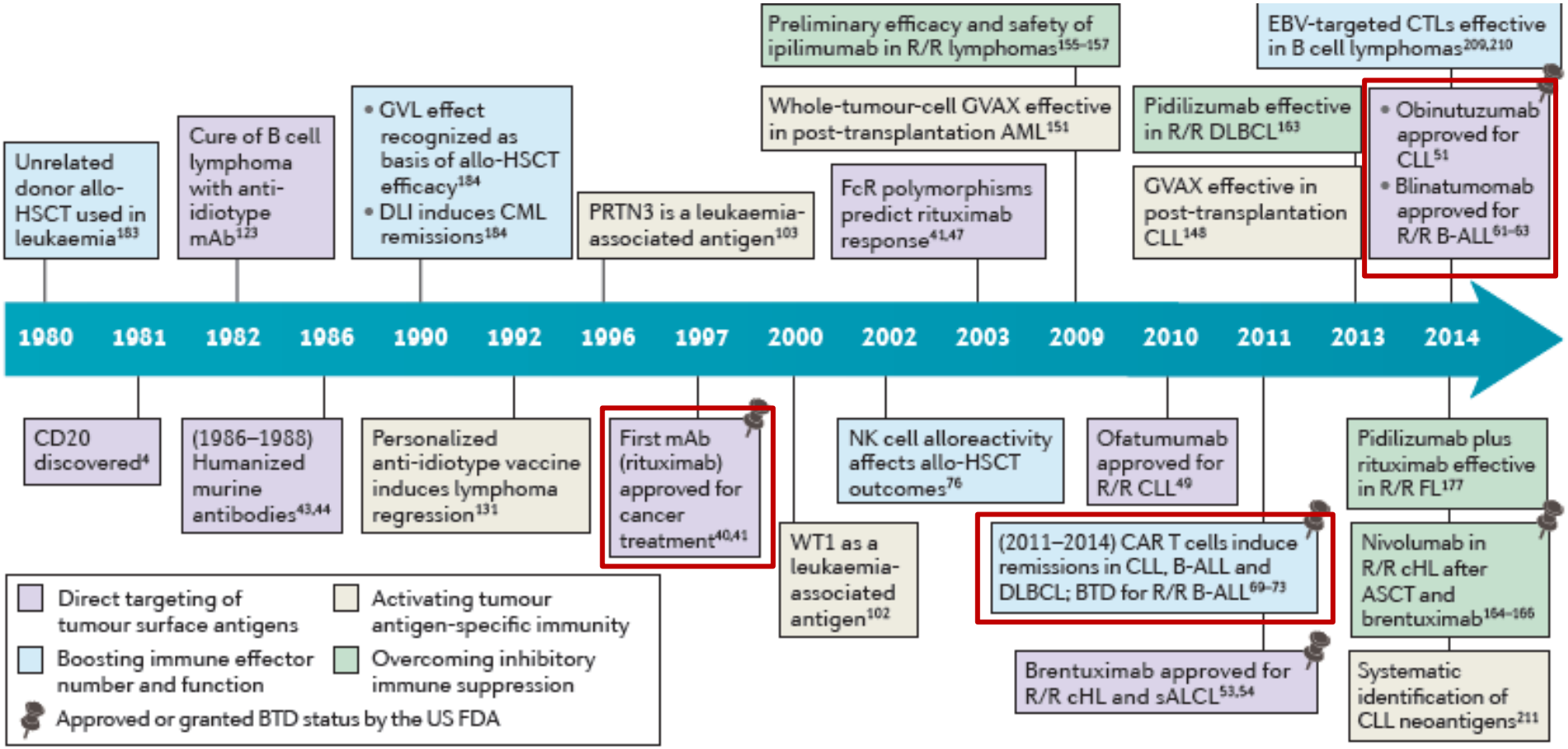


Figure 2 | **Timeline of major immunotherapeutic advances in haematological malignancies.** The figure depicts four areas of

of cancer immunotherapy should yield promising therapeutic combinations. Allo-HSCT, allogeneic haematopoietic stem cell

Table 1 | **Promising clinical immunotherapeutics for haematological malignancies**

Therapeutic class	Agents	Study	Patients	Comments	Clinical approval
Monoclonal antibody	Obinutuzumab	Phase III	Untreated CLL (*n* = 781)	Combination with chlorambucil, compared with combination with rituximab, increased PFS and showed MRD⁻	In combination with chlorambucil for untreated CLL
	Daratumumab	Phase I/II	Relapsed or refractory MM (*n* = 32)	• 31% ORR in all patients • 67% ORR at target PK dose	FDA breakthrough therapy designation for relapsed or refractory MM
Bispecific T cell engager	Blinatumomab	Phase II	MRD⁺ B-ALL (*n* = 21)	80% MRD⁻	Relapsed or refractory Ph⁻ B-ALL
			Relapsed B-ALL (*n* = 36)	69% CR or CRh	
			Relapsed or refractory B-ALL (*n* = 189)	43% CR or CRh	
Adoptive cellular therapy	CAR T cells	Phase I	Relapsed or refractory NHL (*n* = 15)	53% CR; 27% PR	FDA breakthrough therapy designation for relapsed or refractory B-ALL
			Relapsed or refractory B-ALL or T-ALL* (*n* = 30)	90% CR; 78% OS at 6 months	
			Relapsed or refractory B-ALL (*n* = 16)	88% CR or CRh	
	EBV-targeted CTLs	Phase II	High-risk disease (*n* = 29)	97% with NED at 3 years	Not approved
			Relapsed or refractory EBV⁺ NHL or HL (*n* = 21)	62% ORR; 52% CR	
In situ vaccination	Intratumoural TLR9 agonist and low-dose RT	Phase I/II	Indolent NHL (*n* = 15)	1 CR; 3 PR; 2 SD (but continually regressing)	Not approved
Multi-epitope vaccination	Whole-tumour-cell plus GM-CSF vaccination post RIC allo-HSCT	Phase I	High-risk MDS or AML (*n* = 28)	9 out of 15 in CR at 2 years	Not approved
			Advanced CLL (*n* = 22)	88% OS at 2 years (for evaluable patients)	
Immune checkpoint blockade	Pidilizumab	Phase II	Relapsed or refractory DLBCL status post ASCT (*n* = 66)	51% ORR; 34% CR	FDA breakthrough therapy designation for relapsed or refractory HL status post ASCT and brentuximab (for nivolumab)
	Pidilizumab with rituximab	Phase II	Relapsed or refractory FL (*n* = 32)	52% CR	
	Nivolumab	Phase I	Relapsed or refractory cHL status post ASCT (*n* = 23)	87% ORR; 17% CR	

Tratamento do câncer atual

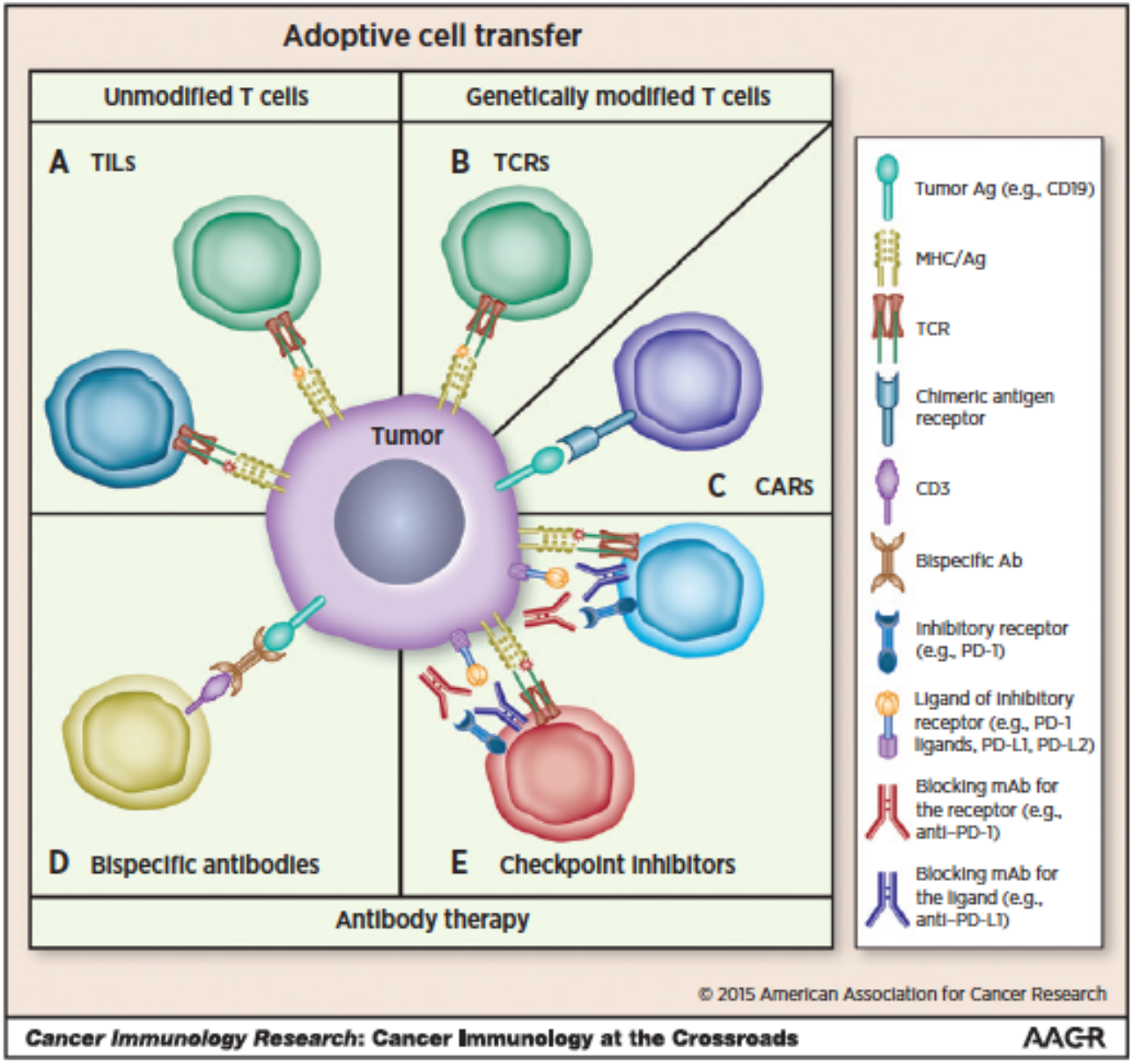


Figure 2.
Strategies for use of T-cell therapies for cancer. Anticancer T-cell–based therapy can be performed (A, D) by *ex vivo* manipulation of T cells through ACT of unmodified (TILs) or genetically modified T cells (TCRs, CARs) and (B, D) by *in vivo* manipulation of T cells using antibodies (bispecific and checkpoint inhibitors). These approaches may induce monoclonal (TCRs, CARs, bispecific antibodies) or polyclonal (TILs, checkpoint inhibitors) antitumor T cells. Ag, antigen.

Immunotherapeutic Biologic Agents in Autoimmune and Autoinflammatory Diseases

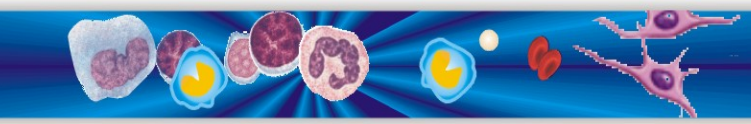
Barbara E. Ostrov

Table 5. Immunotherapeutic agents approved for use in autoimmune and autoinflammatory diseases (adapted from Lefranc, 2015; O'Shea, 2014; Ostrov, 2013).

Generic name	Brand name	Clinical use	Type	Target and mechanism of action
Abatacept	Orencia	RA, polyarticular JIA	CTLA-4 co-stimulatory blocker	CD28 inhibition
Adalimumab	Humira	RA, Psoriasis, AS, PsA, CrD, JIA	Human MAB	Inhibits TNF-α
Anakinra	Kineret	RA, CAPS	Recombinant protein	IL-1 receptor antagonist
Belimumab	Benlysta	SLE	Human MAB	Inhibits BLyS
Canakinumab	Ilaris	CAPS, JIA	Human MAB	Inhibits IL-1β
Certolizumab	Cimzia	RA, AS, PsA, CrD	Humanized FAB	Inhibits TNF-α
Etanercept	Enbrel	RA, JIA, Psoriasis, PsA, AS	Fusion receptor	Soluble TNFα receptor antagonist
Golimumab	Simponi	RA, Psoriasis, AS, PsA, CrD, UC	Human MAB	Inhibits TNF-α
Infliximab	Remicade	RA, AS, PsA, UC, CrD	Chimeric MAB	Inhibits TNF-α
IFN β 1a	Rebif	MS	Cytokine inhibitor	Targets Type 1 IFN
IFN β 1b	Betaseron	MS	Cytokine inhibitor	Targets Type 1 IFN
IFN β 1a	Avonex	MS	Cytokine inhibitor	Targets Type 1 IFN
Natalizumab	Tysabri	CrD, MS	Humanized MAB	Inhibits Integrin α-4
Rilonocept	Arcalyst	CAPS	Fusion receptor protein	Targets IL-1R1/IL-RAcP heterodimeric receptor
Rituximab	Rituxan	RA, ANCA associated vasculitis	Chimeric MAB	Inhibits CD20 receptor on B cells
Tocilizumab	Actemra	RA, polyarticular JIA, Systemic JIA	Humanized MAB	Inhibits IL-6 receptor
Tofacitinib	Xeljanz	RA	Small molecule; Janus kinase inhibitor	Specifically blocks JAK-STAT pathway
Ustekinumab	Stelara	Psoriasis, CrD	Humanized MAB	Anti-p40 antibody; Inhibits Th1/Th17 cells

MAB: monoclonal antibody, JAK: Janus kinase, IFN: interferon, FAB: antibody fragment, CTLA: cytotoxic T lymphocyte-associated protein-4, TNF: tumor necrosis factor, RA: Rheumatoid arthritis, AS: ankylosing spondylitis, SLE: systemic lupus erythematosus, JIA: juvenile idiopathic, MS: Multiple Sclerosis, PsA: Psoriatic arthritis, CAPS: cryopyrin associated periodic syndromes, CrD: Crohn Disease, BLyS: B lymphocyte stimulator, UC: ulcerative colitis.

Immunological Investigations, 2015; 44(8): 777–802



Imunoterapia celular

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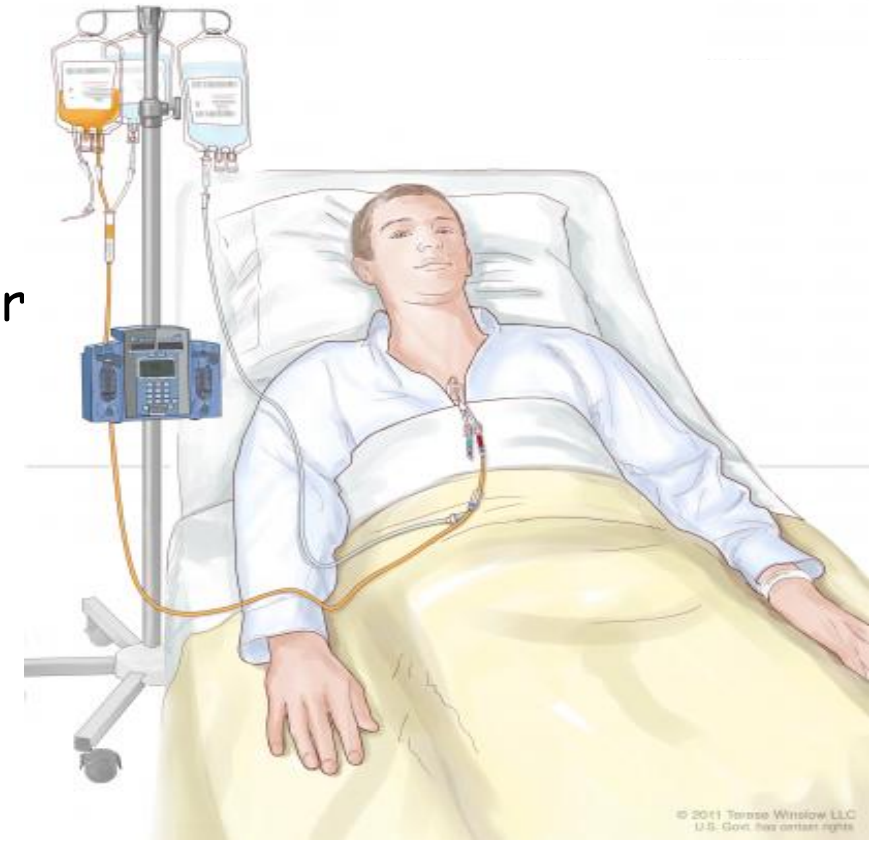
- Células T:
  - ✓ totais (DLI, *donor lymphocyte infusion*)
  - ✓ CAR-T cells
  - ✓ antígeno-específicas (anti-tumor anti-virais)
  - ✓ reguladoras
- Células dendríticas ("vacinas celulares")
- Células NK
- Células estromais mesenquimais



Sacher RA, Cellular Therapy: New Frontiers in Transfusion Medicine, 2003

Imunoterapia celular: células T

Adoptive immunotherapy for cancer: harnessing the T cell response

Nicholas P. Restifo, Mark E. Dudley and Steven A. Rosenberg

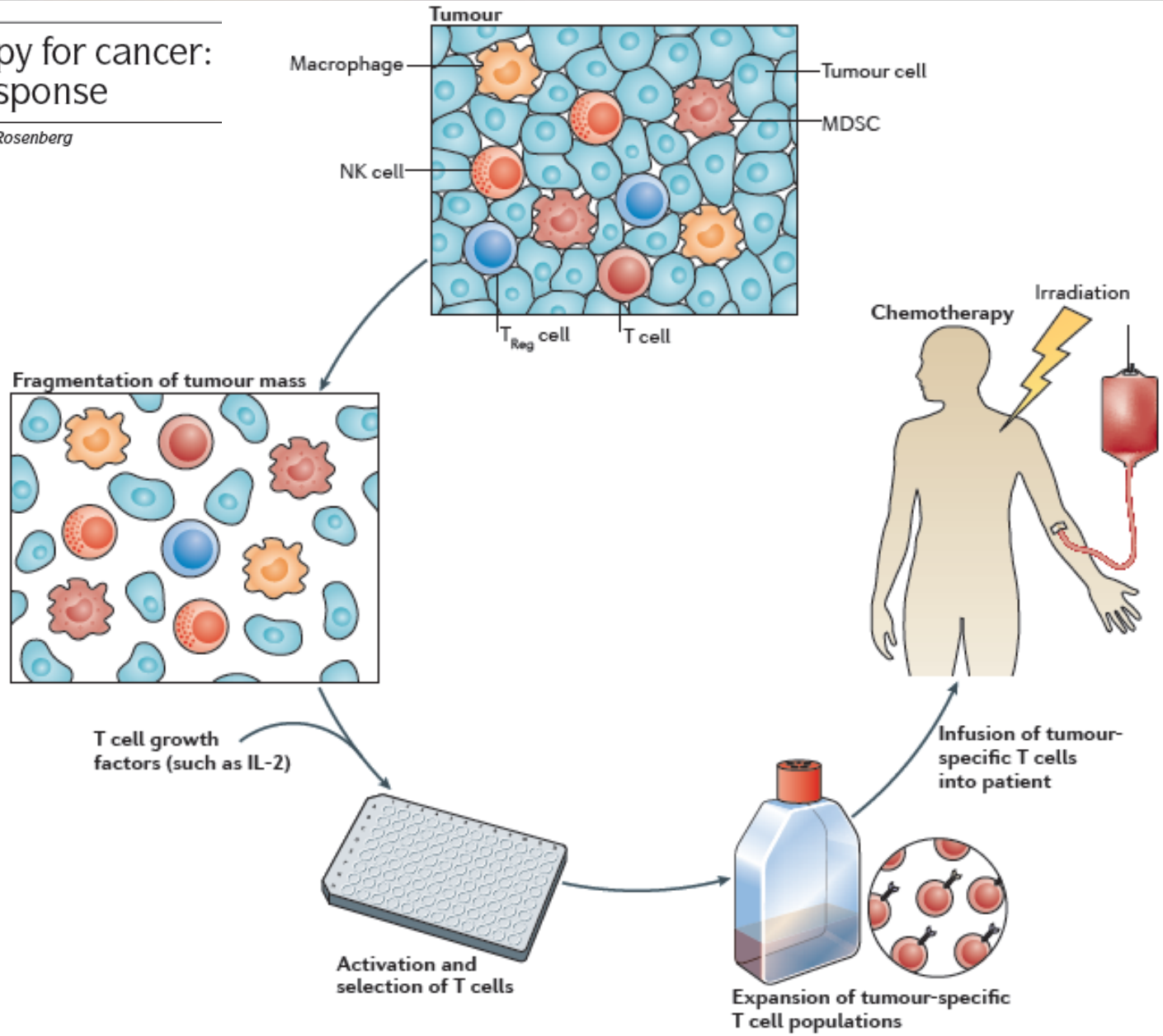


Figure 1 | **Isolation of tumour-infiltrating lymphocytes and expansion of tumour-specific T cell populations.**

Restifo NP *et al.*, Nature Review Immunology (Vol 12), 2012

Imunoterapia com células T: CARs

Chimeric Antigen Receptor Therapy for Cancer

David M. Barrett, Nathan Singh, David L. Porter, Stephan A. Grupp, and Carl H. June

CAR: chimeric antigen receptor

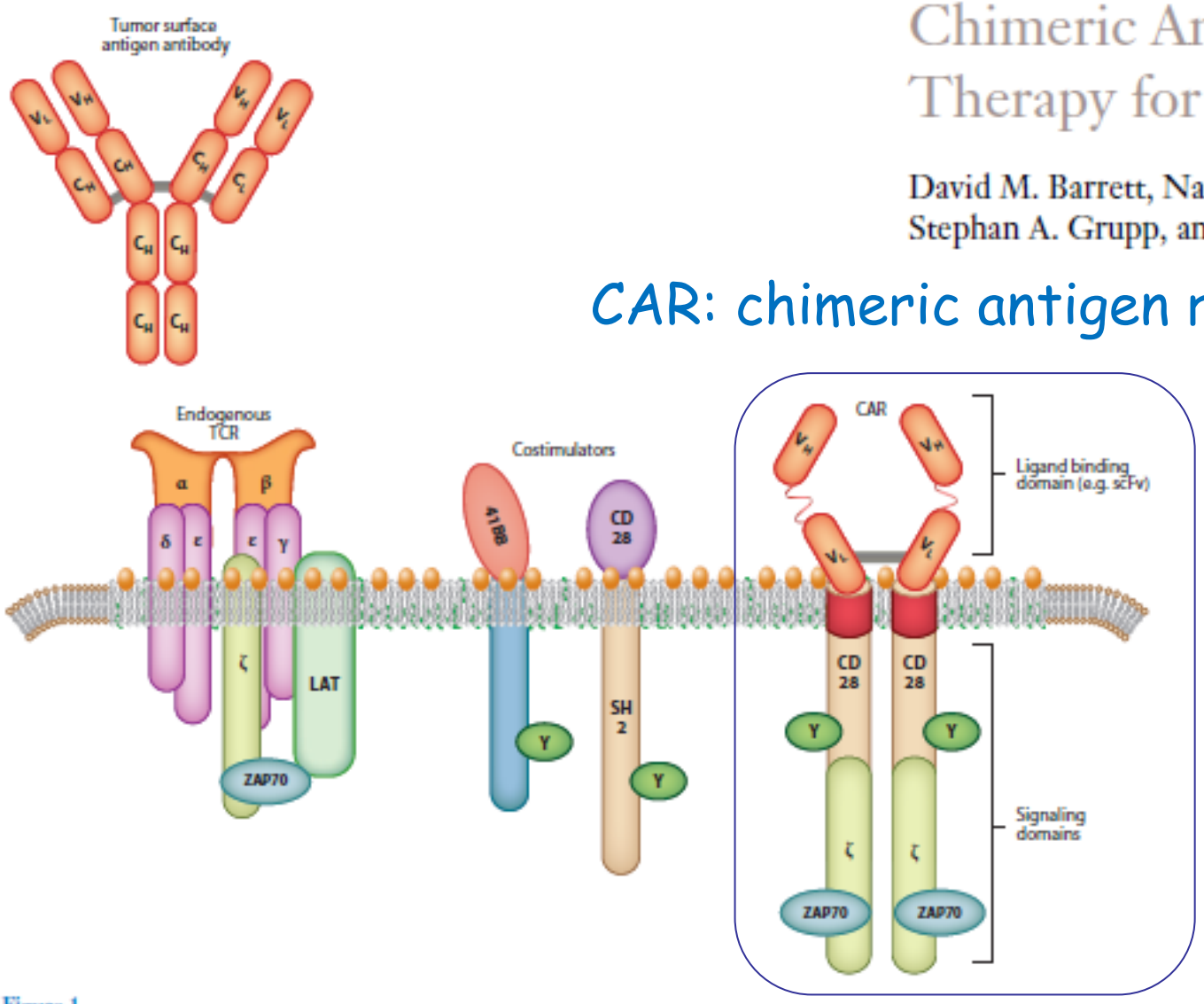
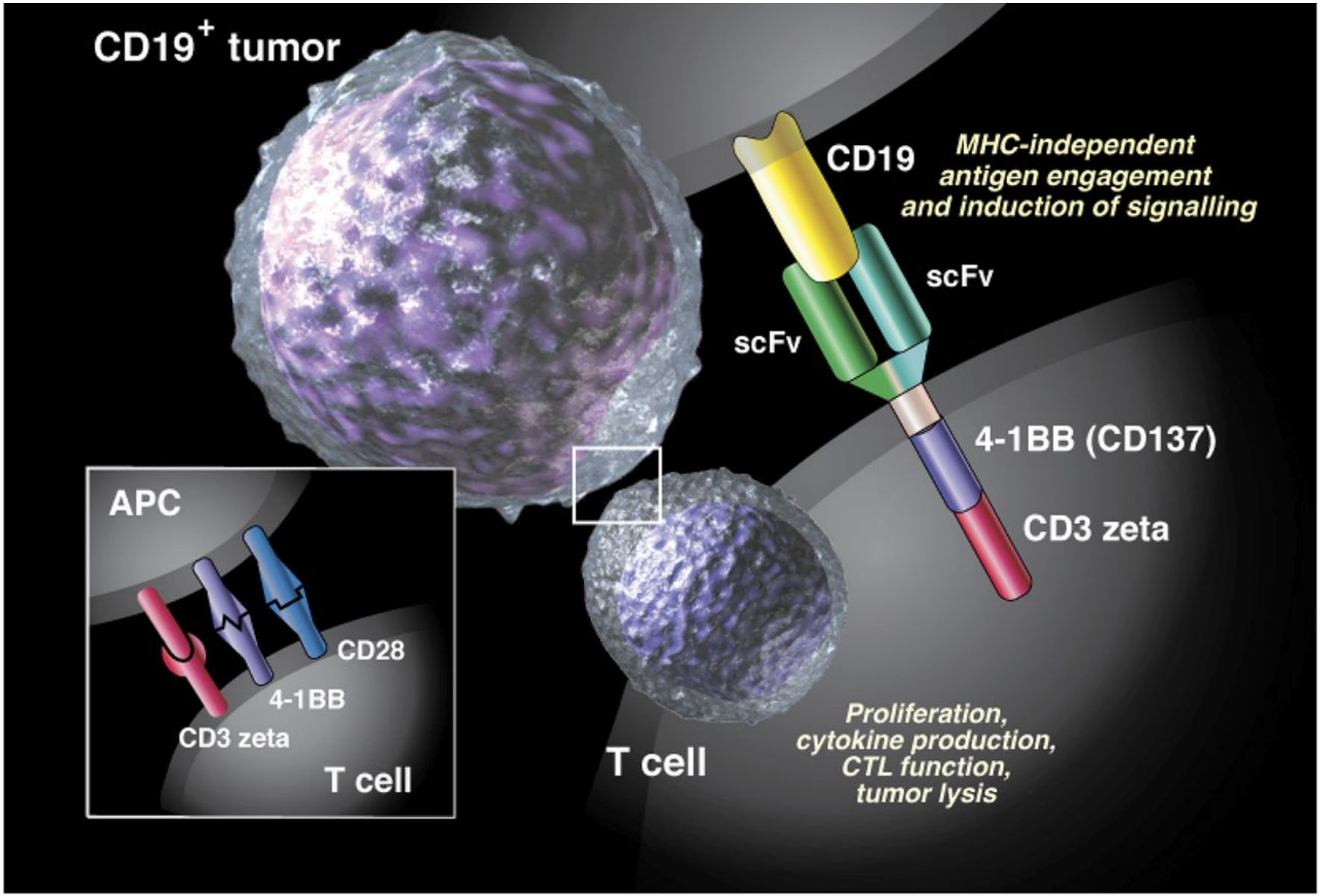


Figure 1

Antibodies can bind to surface antigens expressed on tumor cells. Chimeric antigen receptors (CARs) have a single-chain antibody fragment (scFv), expressed in tandem with signaling elements derived from the T cell receptor (TCR) and costimulatory domains such as 4-1BB and CD28.

Annu. Rev. Med. 2014.65:333-347

Imunoterapia com células T-CAR



Annu. Rev. Med. 2014.65:333-347.

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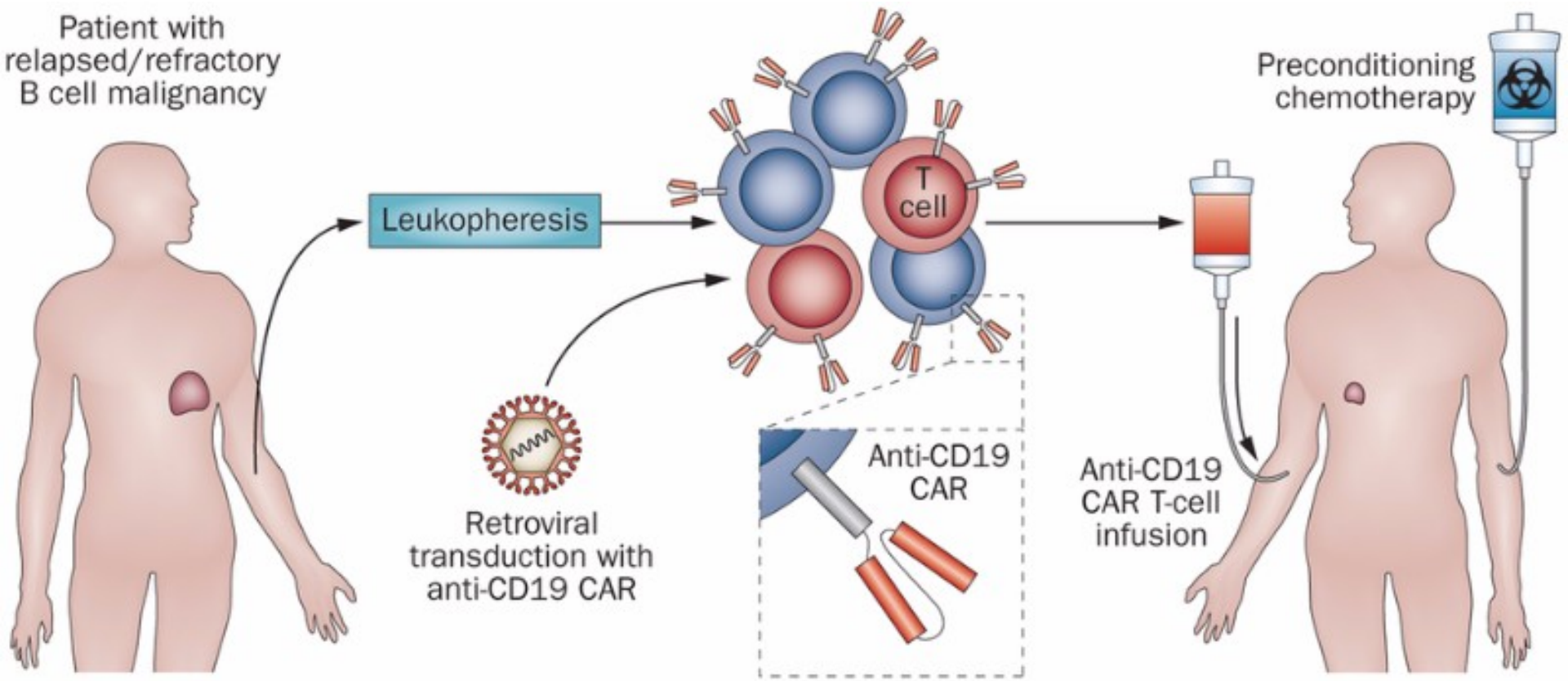

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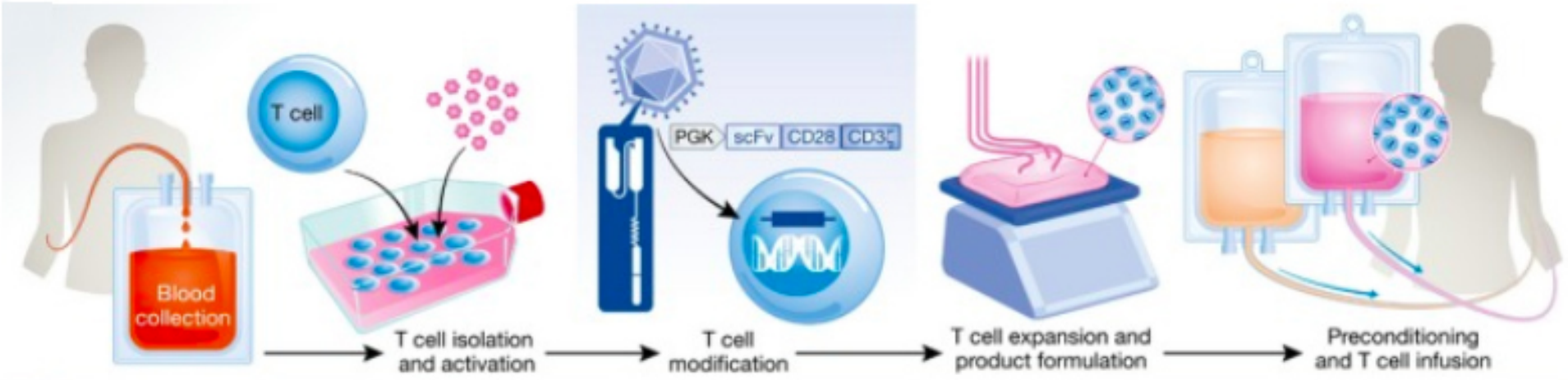

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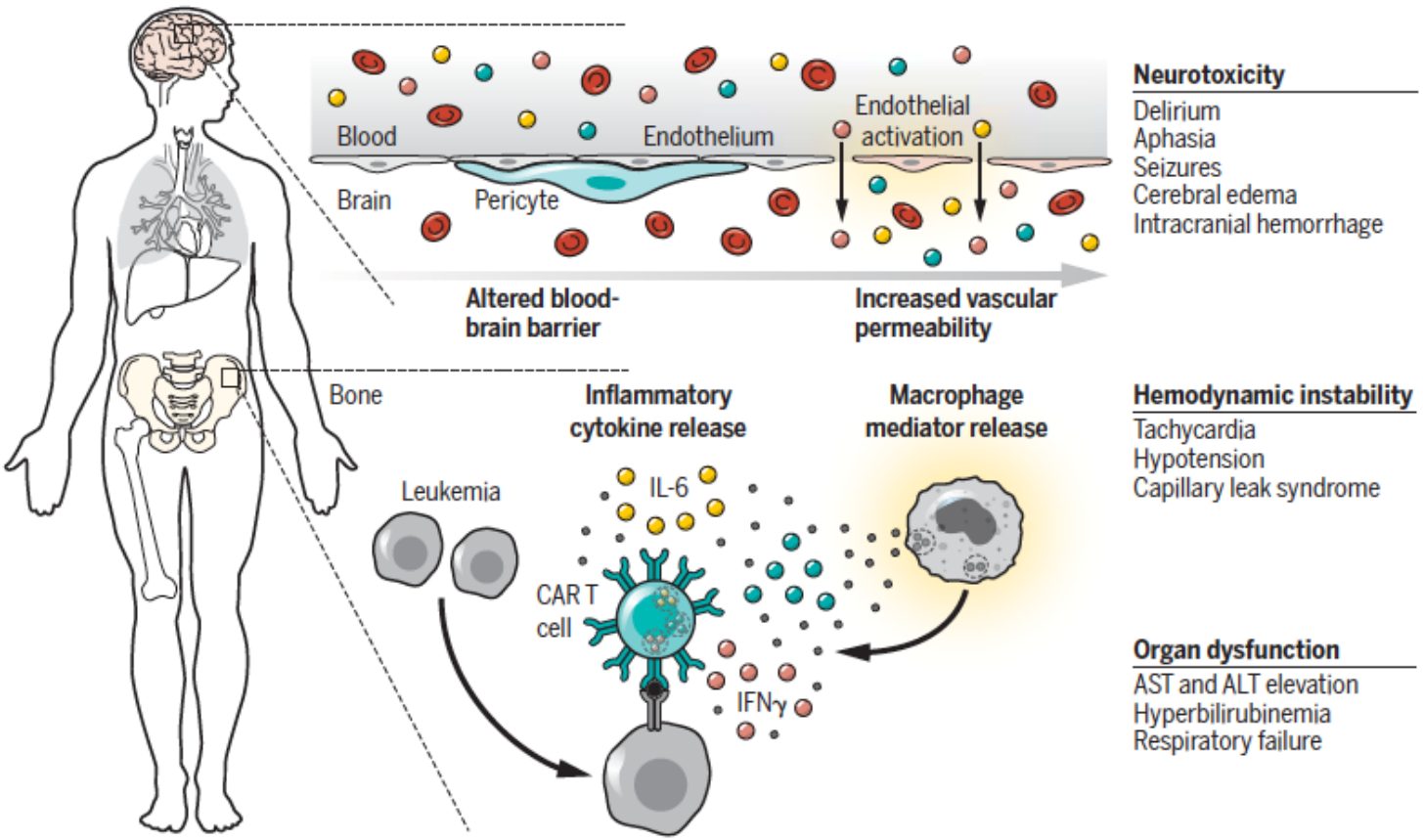
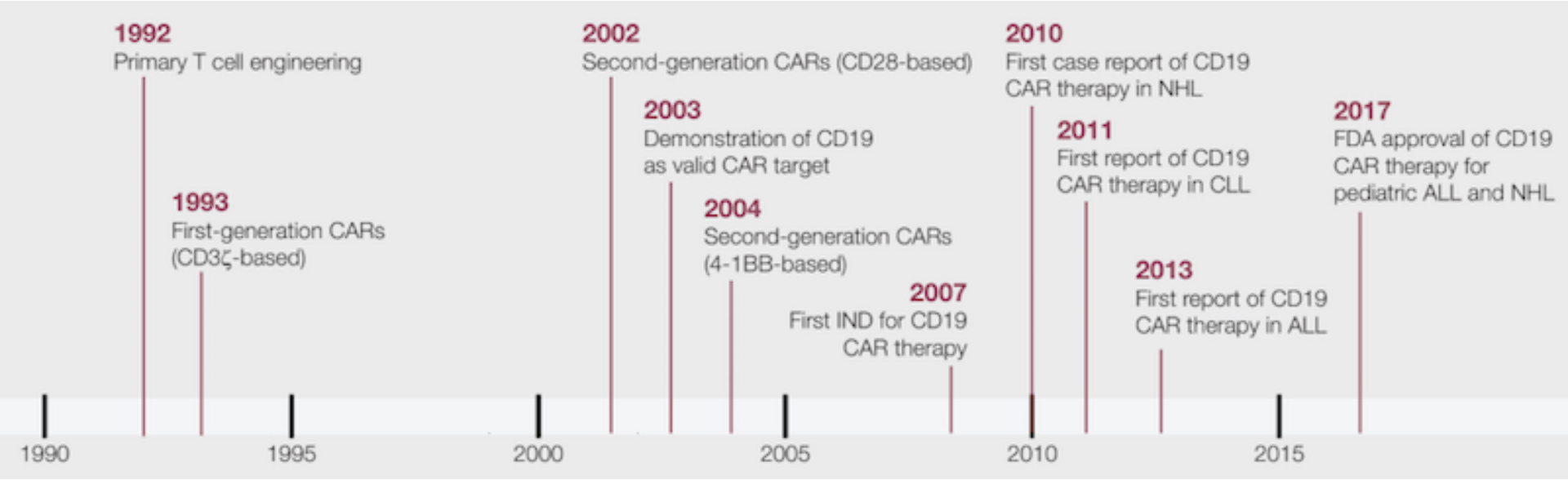


Fig. 2. CAR T cell therapy is associated with cytokine release syndrome and neurotoxicity. Cytokine release syndrome has occurred with CAR T cells targeting CD19 or BCMA. When the CAR T cell engages surrogate antigens, it releases a variety of cytokines and chemokines. Macrophages and other cells of the innate immune system also become activated and contribute to the release of soluble mediators. CAR T cells are routinely observed in cerebral spinal fluid, and the cytokines may increase permeability to soluble mediators and permit increased trafficking of CAR T cells and other lymphocytes to central nervous system parenchyma. IFN, interferon; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

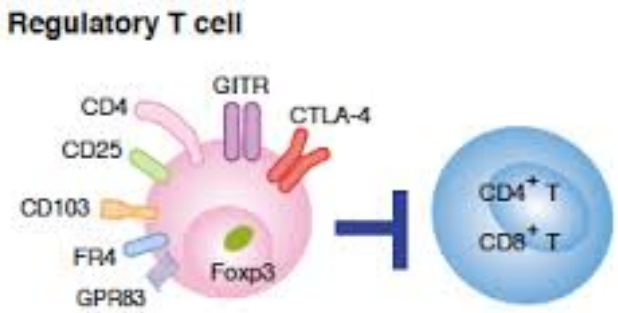
Imunoterapia com células CAR-T

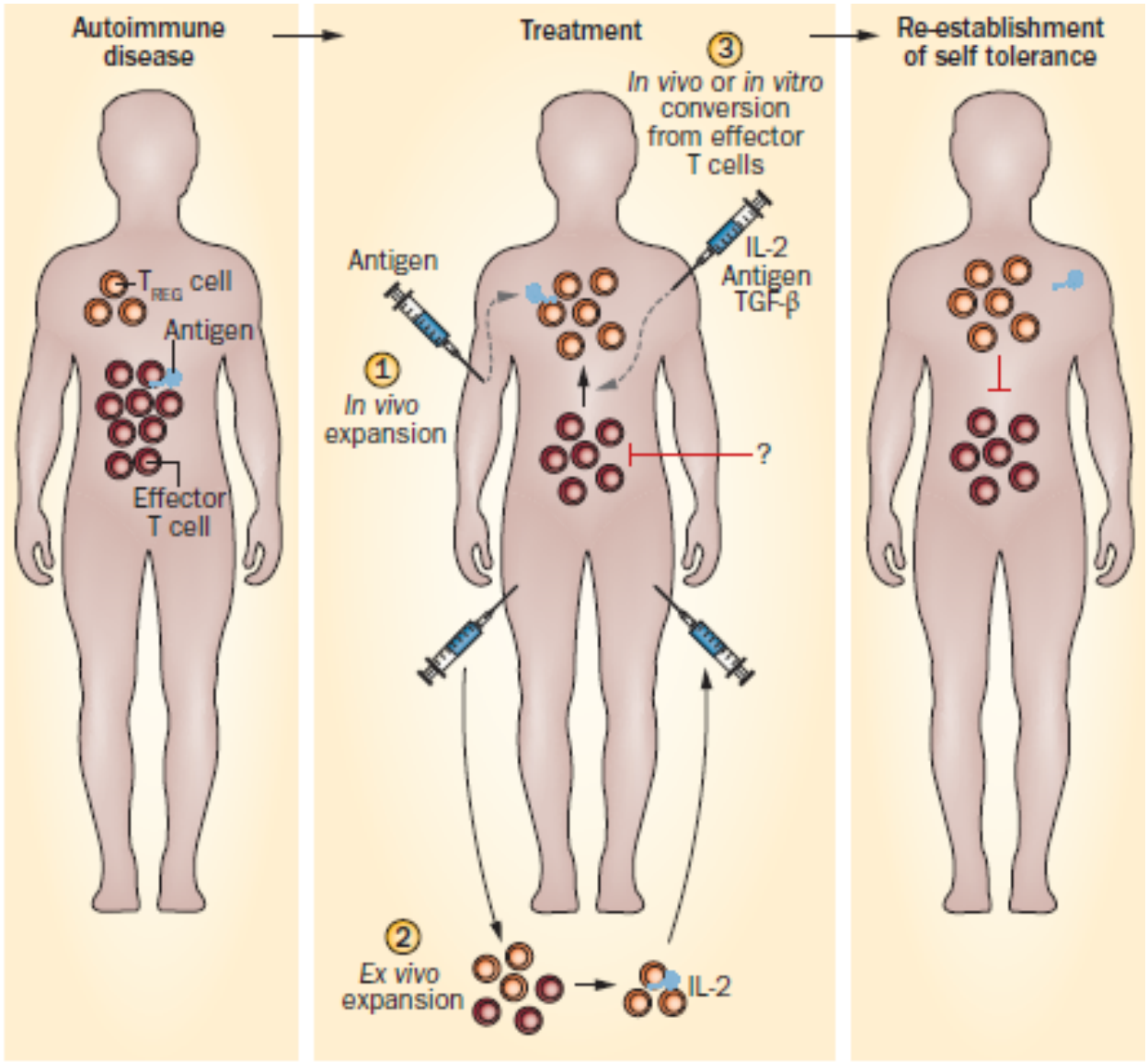


Imunoterapia: Tregs

T_{REG}-cell therapies for autoimmune rheumatic diseases

Makoto Miyara, Yoshinaga Ito and Shimon Sakaguchi





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Imunoterapia: Tregs

Tregs: células T reguladoras

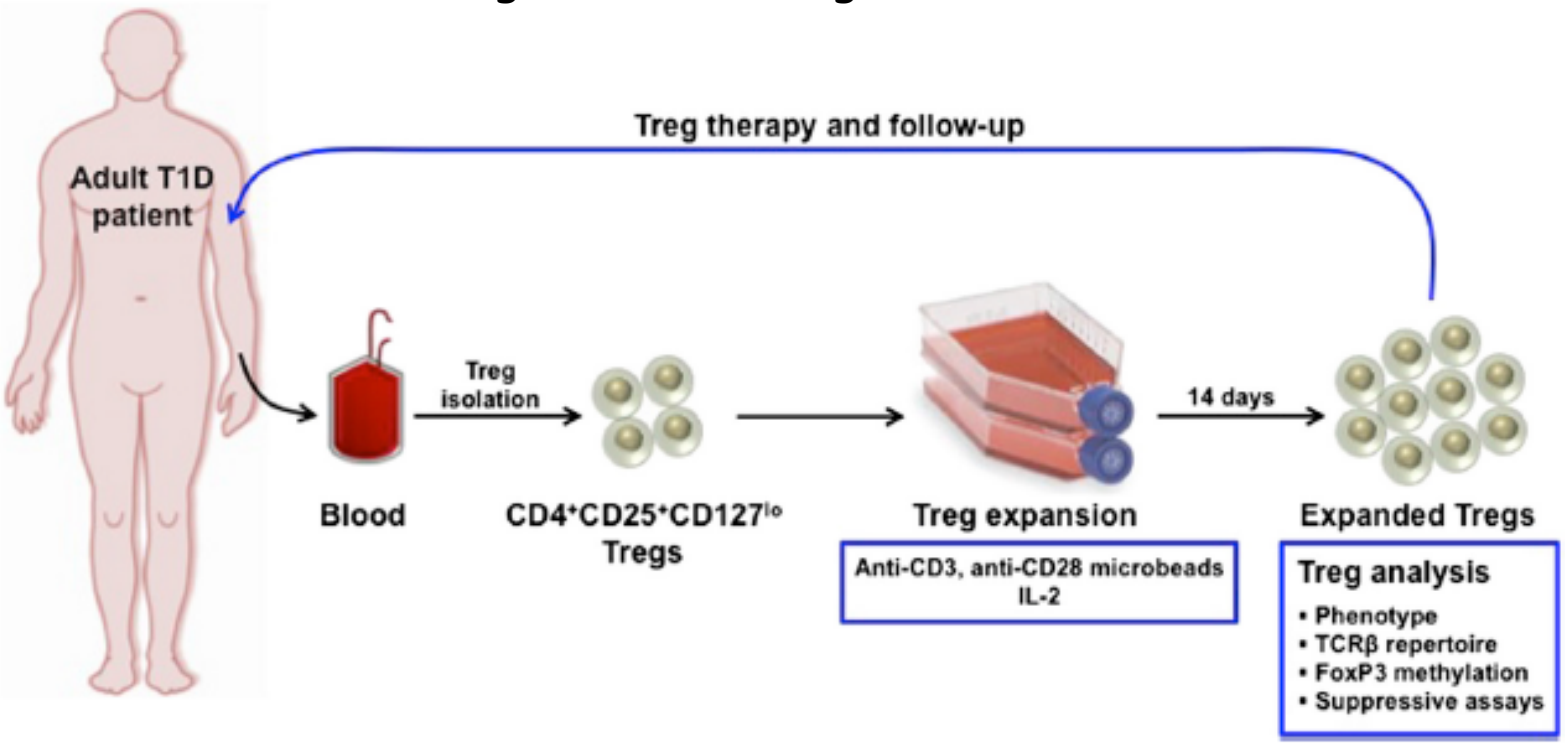
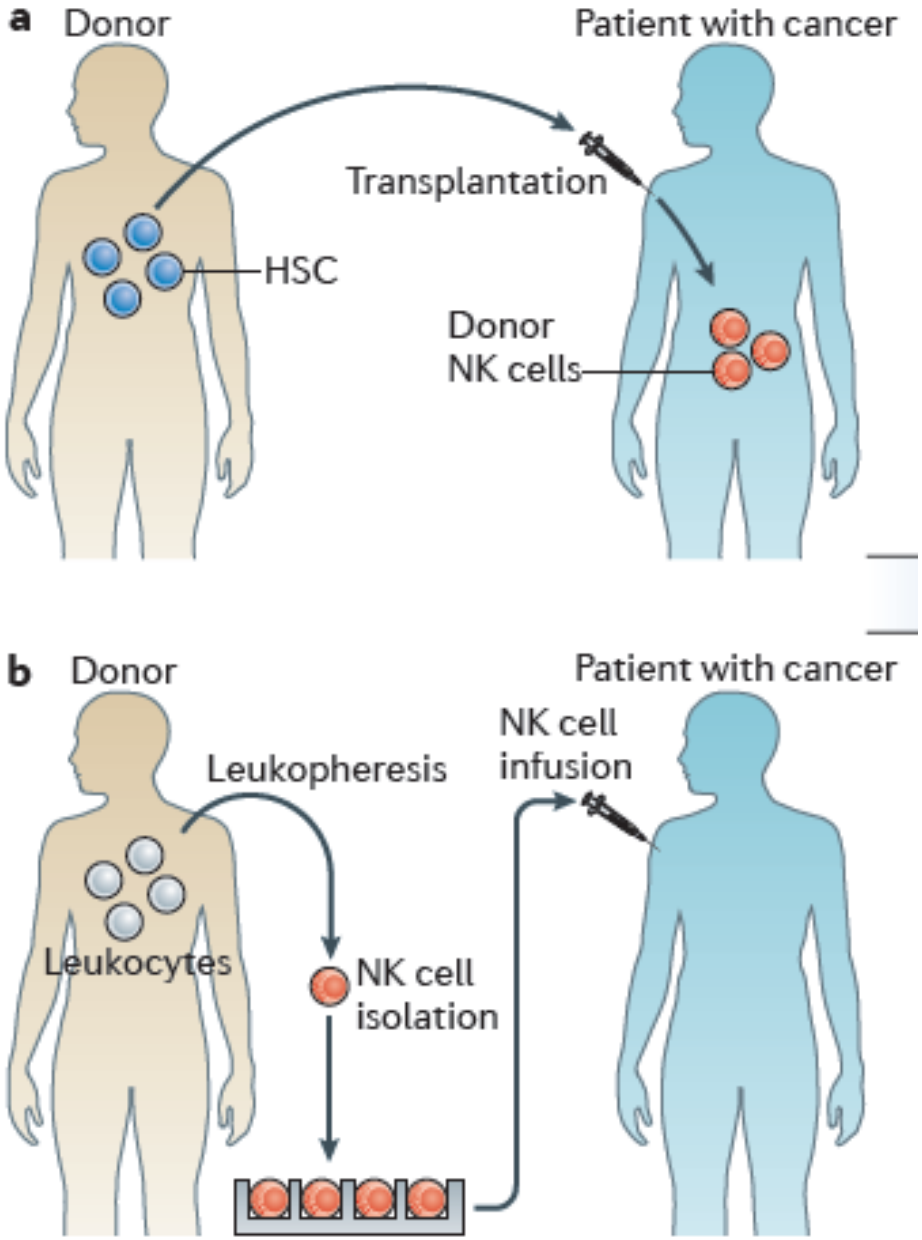


Figure 1. Scheme of Ex Vivo-Expanded Autologous Polyclonal Regulatory T Cell Therapy in Adult Type 1 Diabetes

Bluestone et al. (2015) collected 400 ml of blood from patients with recent-onset adult T1D. $CD4^+CD25^+CD127^{lo}$ regulatory T cells (Tregs) were sorted and expanded for 14 days. Following detailed analysis of expanded Tregs, patients received a single dose of Tregs. During the follow up, patients were assessed for safety and immunological and metabolic parameters. Tracking of adoptively transferred Tregs was also performed.

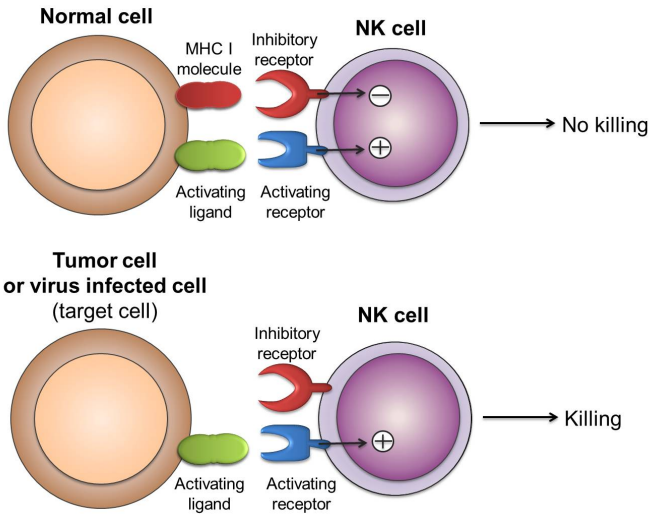
Cell Metabolism 23, February 9, 2016

Imunoterapia celular: células NK



Therapeutic approaches to enhance natural killer cell cytotoxicity against cancer: the force awakens

Richard W. Childs and Mattias Carlsten



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Imunoterapia celular: DCs

Clinical use of dendritic cells for cancer therapy

Sébastien Anguille, Evelien L Smits, Eva Lion, Viggo F van Tendeloo, Zwi N Berneman

	Dendritic cell product	Control group	Status	ClinicalTrials.gov identifier
Melanoma	Autologous monocyte-derived DCs pulsed with melanoma peptides Autologous DCs mixed with irradiated autologous tumour cells suspended in GM-CSF (melapuldencel-T)	Dacarbazine Autologous PBMCs suspended in GM-CSF	Completed Not yet recruiting	NA[5] NCT01875653
Prostate	Autologous APCs (including DCs) loaded with PAP/GM-CSF (sipuleucel-T)	Autologous APCs	Completed	NCT00005947 NCT00065442 NCT00779402 NCT01133704
Brain (GBM)	Autologous DCs pulsed with autologous tumour lysate (DC-VAX-L)	Autologous PBMCs	Recruiting	NCT00045968
Renal	Autologous DCs electroporated with autologous tumour mRNA and CD40L mRNA, in combination with sunitinib (AGS-003)	Sunitinib	Recruiting	NCT01582672

Excludes one study in prostate cancer that was withdrawn before enrolment (NCT00043212) and three studies with phase 2/3 design (NCT01759810, NCT01782274, and NCT01782287). DCs=dendritic cells. GM-CSF=granulocyte macrophage colony-stimulating factor. PBMCs=peripheral blood mononuclear cells. APCs=antigen-presenting cells. PAP/GM-CSF=chimeric antigen consisting of the prostate tumour antigen prostatic acid phosphatase (PAP) linked to GM-CSF. GBM=glioblastoma multiforme. NA=not available.

Table 1: **Overview of completed and ongoing randomised phase 3 clinical trials of dendritic cell-based cancer immunotherapy, by cancer type**

Imunoterapia celular: DCs

Clinical use of dendritic cells for cancer therapy

Sébastien Anguille, Evelien L Smits, Eva Lion, Viggo F van Tendeloo, Zwi N Berneman

	Evidence level	Overall survival			Dendritic cell product	
		DC group (months)	Control group (months)	% change	Dendritic cell type	Activation
Melanoma						
N=11[21]	III-3	9·3	4·0	+133%	IL-4 moDCs	MCM
N=13[22]	III-1	6·2	14·8	−58%	IL-4 moDCs	Immature
N=54[23-25]	III-1	64·0	31·0	+107%	IL-4 moDCs	GM-CSF
N=17[26]	III-3	22·4	8·0	+180%	IL-4 moDCs	TNF-α
N=11[27]	III-3	7·3	4·0	+83%	IL-4 moDCs	TNF-α/IL-1β/IL-6/PGE2
N=16/22*[28]	III-2	12·3	5·8	+112%	IL-4 moDCs	TNF-α/IL-1β/IL-6/PGE2
N=20[29,30]	III-3	8·6	4·0	+115%	IL-4 moDCs	TNF-α+Poly(I:C)
N=53[5]	II	9·3	11·6	−20%	IL-4 moDCs	TNF-α/IL-1β/IL-6/PGE2
N=34[31]	III-3	18·5	11·6	+60%	IL-4 moDCs	TNF-α/IL-1β/IL-6/PGE2
N=28[32]	III-3	9·4	5·1	+84%	IL-4 moDCs	TNF-α/IL-1β/IL-6/PGE2
N=24[33]	III-3	13·6	7·3	+86%	IL-4 moDCs	Immature
N=29[34]	III-3	15·0	8·3	+81%	IL-4 moDCs	TNF-α/PGE2
N=15[35]	III-3	22·0	7·6	+189%	Natural pDCs	FSME-IMMUN
Prostate						
N=33[36-38]	III-3	>20·0	6·0	+233%	IL-4 moDCs	Immature
N=147/225[39,40]	II	23·2	18·9	+23%	Sipuleucel-T	GM-CSF
N=12[41]	III-3	21·0	12–19	+10–75%	IL-4 moDCs	TNF-α/PGE2
N=341/512[42]	II	25·8	21·7	+19%	Sipuleucel-T	GM-CSF

Imunoterapia celular: células NK

Table 2 | **Clinical studies evaluating the efficacy of adoptively infused NK cells**

Method	Patient population	Total number of clinical trials (number of active trials)	Comments
Non-expanded NK cells			
Autologous NK cells + IL-2	Melanoma, RCC, lung cancer and nasopharyngeal cancer	3 (1)	–
Autologous NK cells + IL-15	Neuroblastoma, sarcoma, Wilms tumour and rhabdomyosarcoma	1 (1)	Intended to more specifically bolster NK cell antitumour activity than IL-2
Allogeneic NK cells + IL-2	AML, multiple myeloma, myelodysplastic syndromes, lymphoma, ovarian carcinoma, melanoma, neuroblastoma, Ewing sarcoma, breast cancer and Fallopian tube cancer	55 (29)	Most data published on adoptive NK cell therapy are from these studies
Allogeneic NK cells + IL-15	AML and myelodysplastic syndromes	2 (1)	Intended to more specifically bolster NK cell antitumour activity than IL-2
Expanded NK cells			
Autologous NK cells	CLL, RCC, lung cancer, multiple myeloma, sarcoma, colon cancer, melanoma, neuroblastoma, prostate cancer, ALL and pancreatic cancer	7 (6)	Various expansion methods used, including EBV-LCL and membrane-bound cytokine or 4-1BBL feeder cells; some studies use IL-2 post NK cell infusion
Allogeneic NK cells	AML, myelodysplastic syndromes, T cell lymphoma and multiple myeloma	11 (8)	Various expansion methods used, including EBV-LCL and membrane-bound cytokine or 4-1BBL feeder cells; some studies use IL-2 post NK cell infusion
Genetically manipulated NK cells			
CD19 CAR mRNA (expanded NK cells)	BCL	2 (2)	Designed to redirect tumour targeting. Haploidentical NK cells expanded with K562 membrane-bound IL-15 or 4-1BBL feeder cells; in Phase II clinical trials
NK cell lines			
NK-92	AML, multiple myeloma and lymphoma	2 (2)	Off-the-shelf NK cells; in dose-escalating Phase I clinical trials

Imunoterapia celular: MSCs

Immunoregulatory mechanisms of mesenchymal stem and stromal cells in inflammatory diseases

Yufang Shi[1,2], Yu Wang[2], Qing Li[2], Keli Liu[2], Jianquan Hou[1], Changshun Shao[1] and Ying Wang[2]**

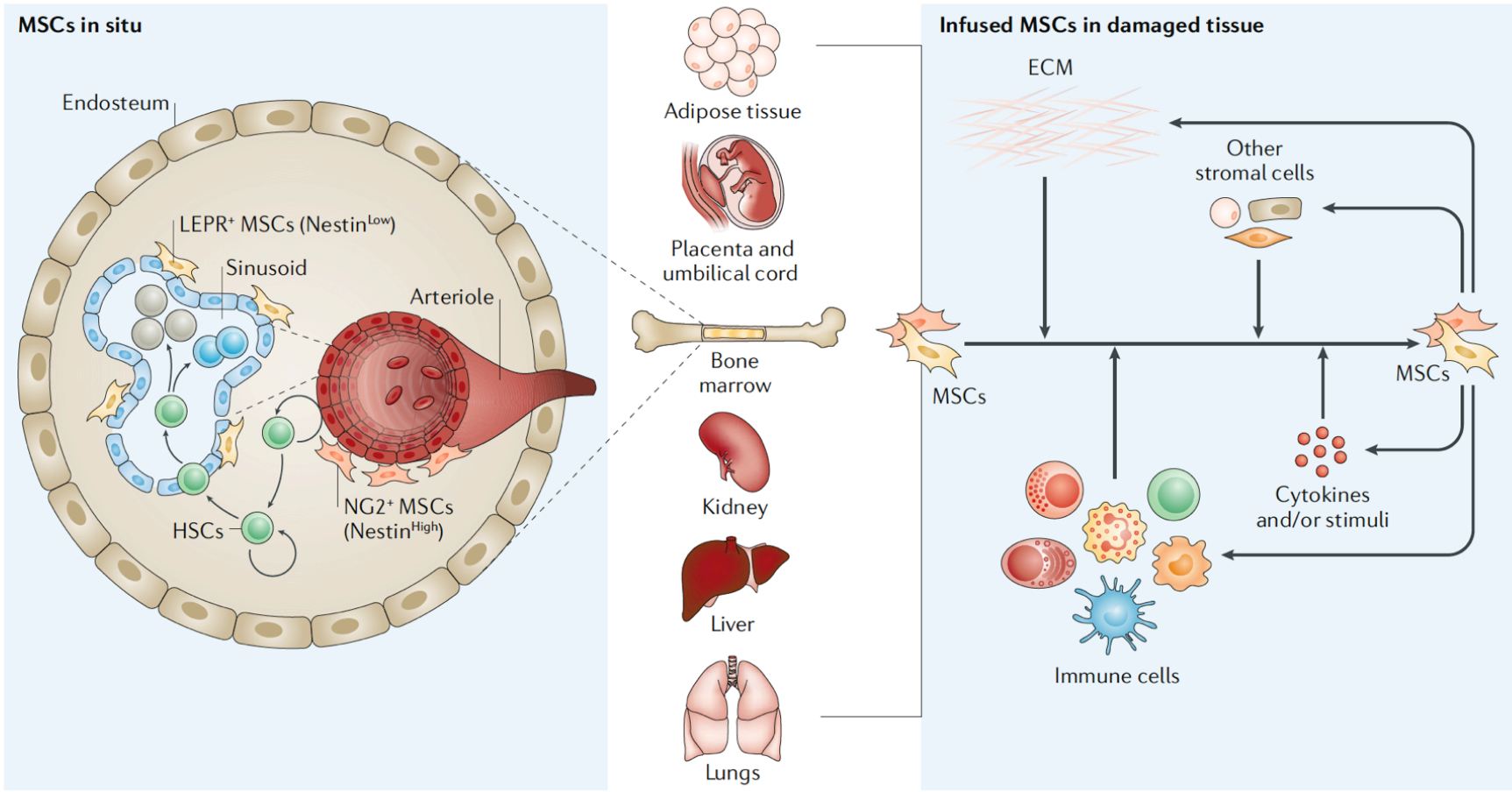
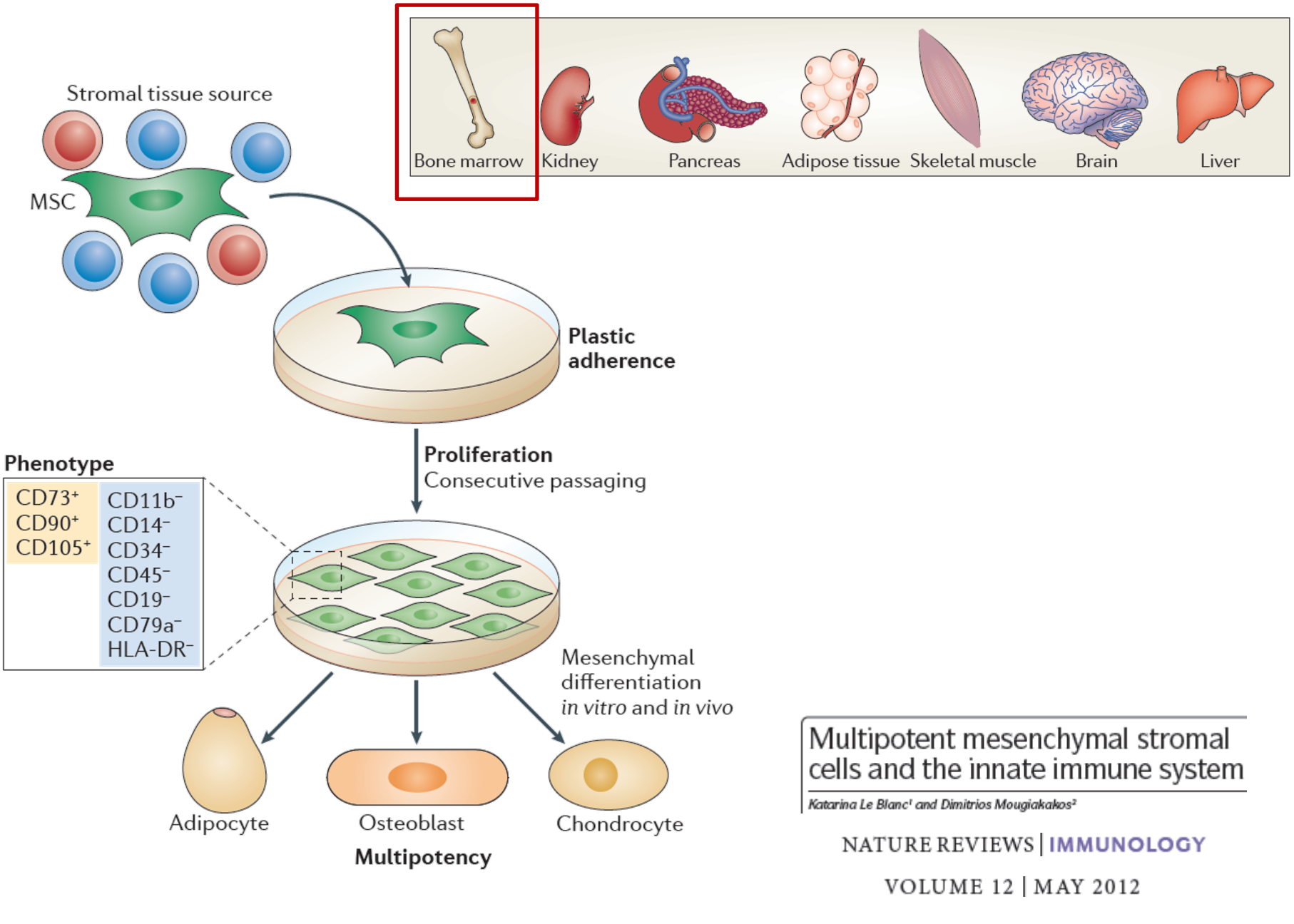


Fig. 1 | **Tissue locations affect the biology of MSCs.** Mesenchymal stem cells (MSCs) have been successfully isolated from multiple tissues, such as bone marrow, adipose tissue, umbilical cord, placenta, kidney, liver and lung. Analyses to

Imunoterapia celular: MSCs



Multipotent mesenchymal stromal cells and the innate immune system

Katarina Le Blanc[1] and Dimitrios Mougiakakos[2]

NATURE REVIEWS | IMMUNOLOGY

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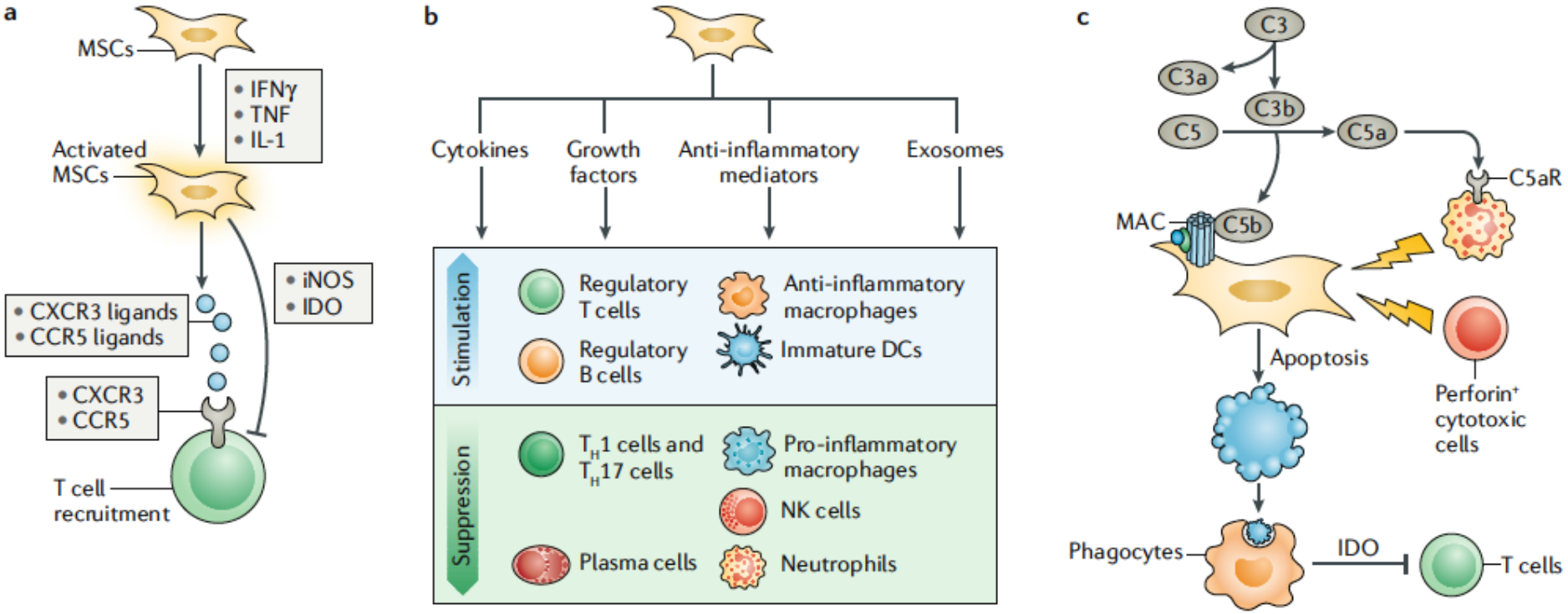

Fig. 2 | **Mechanisms of MSC-mediated immunomodulation.** Mesenchymal stem cells (MSCs) exert immunomodulatory

Imunoterapia celular: MSCs

Table 1. Representative examples of MSC clinical trials in Europe. Asterisks indicate those trials supported by the European Union's health research program. EudraCT, European Clinical Trials Database.

Indication	Indication category	EudraCT no.	Clinical trial	MSC source	Postulated mode of action	Challenges
Perianal fistulas in Crohn's disease	Autoimmune disease	2011-005966-39 www.tigenix.com	Phase 3 randomized controlled trial	Allogeneic adipose-derived	Immuno-modulation	Distinguishing acute vs chronic disease status
*Severe, steroid-refractory acute GvHD	GvHD	2012-004915-30 www.rethrim.eu	Phase 3 randomized controlled trial	Allogeneic bone marrow–derived	Immuno-modulation	Few patients, confounding factors, poor response measures, differences between adults and children
*Critical limb ischemia	Angiogenesis induction	2015-005532-18 www.pace-h2020.eu	Phase 3 randomized controlled trial	Allogeneic placenta-derived	Regeneration	Complex pathophysiology, impact of diabetes on response
*Untreatable ischemic cardiac disease	Cardiac repair	2015-002929-19 http://stemcellscience.dk	Phase 2 randomized controlled trial	Allogeneic adipose-derived	Regeneration	Duration of preexisting condition may affect response
*Knee osteoarthritis	Chronic degenerative disease	2015-002125-19 http://adipoa2.eu	Phase 2b randomized controlled trial	Autologous adipose-derived	Immuno-modulation	Confounding factors, disease clinical course variable
*Non-union long bone fractures	Skeletal tissue repair	2015-000431-32 http://orthounion.eu	Phase 2b randomized controlled trial	Autologous bone marrow–derived	Regeneration	Heterogeneity of clinical cases
*Severe bacterial pneumonia	Infectious disease	2015-002994-39 www.sepcell.eu	Phase 1b/2a randomized controlled trial	Allogeneic adipose-derived	Immuno-modulation	Cell dose is critical
Osteogenesis imperfecta	Genetic disease	2012-002553-38	Phase 1 clinical trial	Allogeneic bone marrow–derived	Regeneration	Clinical course is unpredictable and is difficult to test

Imunoterapia celular: MSCs

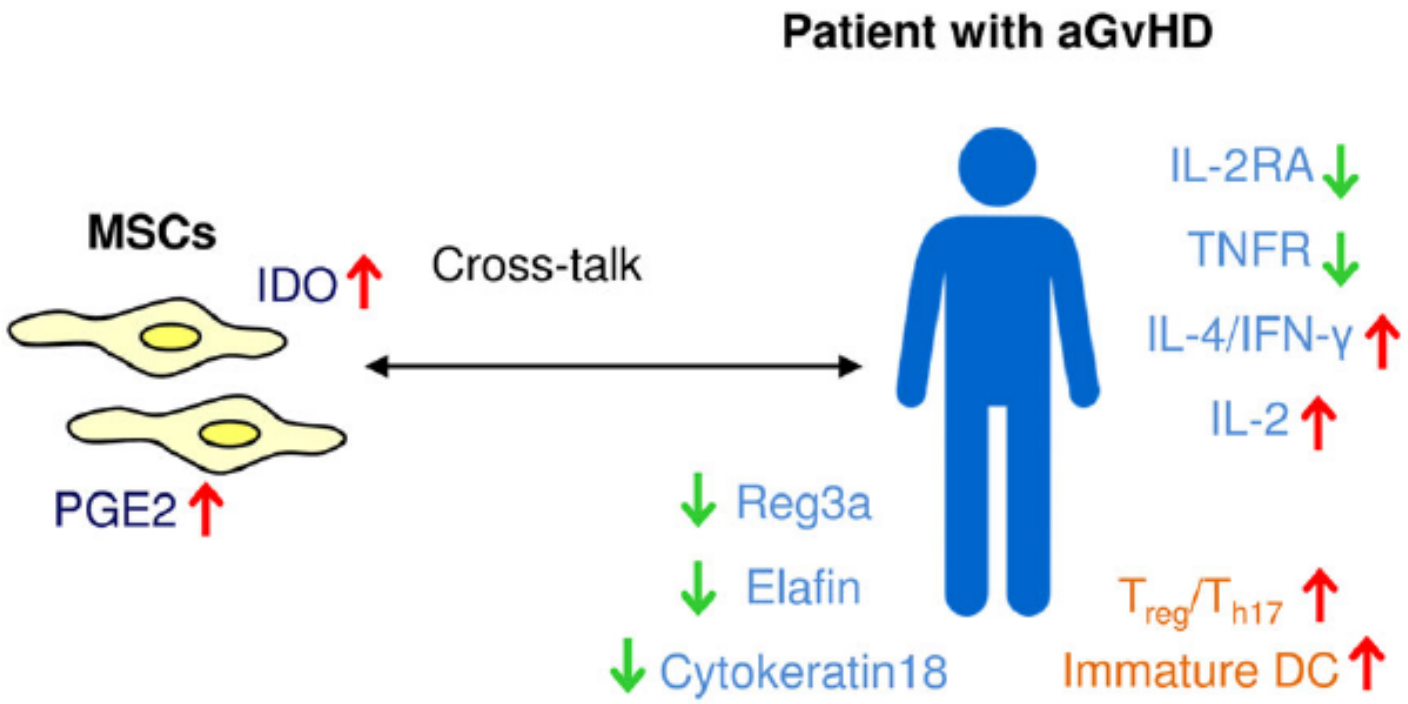

Figure 2. Central role for host–product interaction in the immunomodulatory effect of MSC-mediated immunomodulation in aGvHD. Schematic representation of the cross talk between MSCs and the host, including the proinflamatory molecule–induced changes in the MSCs (in black). On the right, the cellular and molecular changes in the blood of patients with aGvHD that have been treated with MSCs are indicated (in orange and blue, respectively). Green and red arrows indicate downregulation and upregulation.

Imunoterapia celular: MSCs

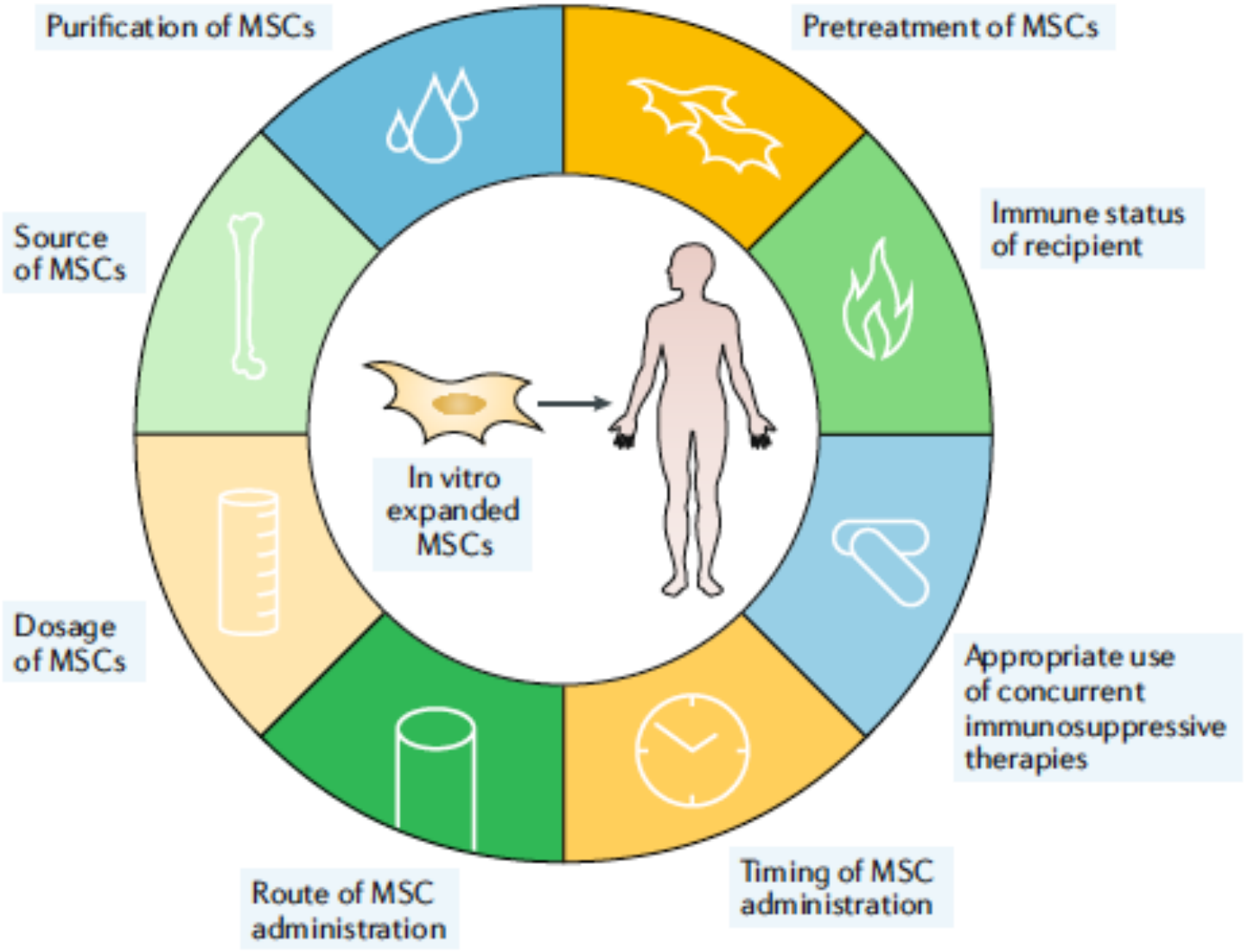

Fig. 4 | **Key considerations for MSC-based clinical applications.** A number of key

Imunoterapia celular

- Laboratórios especializados de terapia celular (GMP facility, Cell Therapy Laboratory)
- Normas "GMP", controle de qualidade, padronização de protocolos, segurança
- Brasil: RDC/Anvisa (requisitos mínimos Centros de Tecnologia Celular)

cGMP Cell Therapy Laboratory,
Northwestern Memorial Hospital

Imunoterapia celular

cGMP Cell Therapy Laboratory ,
Northwestern Memorial Hospital

Empresas biofarmacêuticas

And 700+ Other Companies Worldwide . . .

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Incyte

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OUR COMPANY | WHAT WE DO | FOR INVESTORS | INCYTE NEWS | JOIN OUR TEAM | INCYTE INVOLVED | CONTACT US

Discovery & Development | Partnerships | Therapies & Support | Portfolio

Drug Discovery and Development

At Incyte, our therapeutic focus is primarily oncology. Since we began our drug discovery and development activities in early 2002, we have filed Investigational New Drug (IND) applications and progressed multiple internally developed proprietary compounds into clinical development. In late 2011, we received our first US Food and Drug Administration approval for **Jakafi® (ruxolitinib), a JAK1 and JAK2 inhibitor**.

Incyte has an exceptional team of drug discovery and development scientists, led by distinguished executives with proven records of success and many scientific and clinical achievements. We employ only the best and those who adhere to the highest standards of scientific and clinical rigor, and we resource our programs for success. We have a strong discovery team that is tightly integrated with all disciplines, including development, regulatory, and commercial operations.

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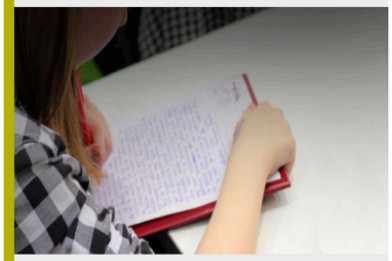
INSTITUTO BUTANTAN
A serviço da vida

Buscar

Atrações
Além do parque, o Instituto conta com diversas atrações abertas ao público.

Ensino
Temos o compromisso de oferecer informação e divulgação científica.

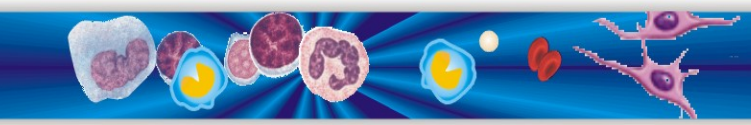


Soros e Vacinas
Somos o principal fornecedor de imunobiológicos do Brasil.

Pesquisa e Inovação
A ciência e a busca por novos conhecimentos são nossas bases.

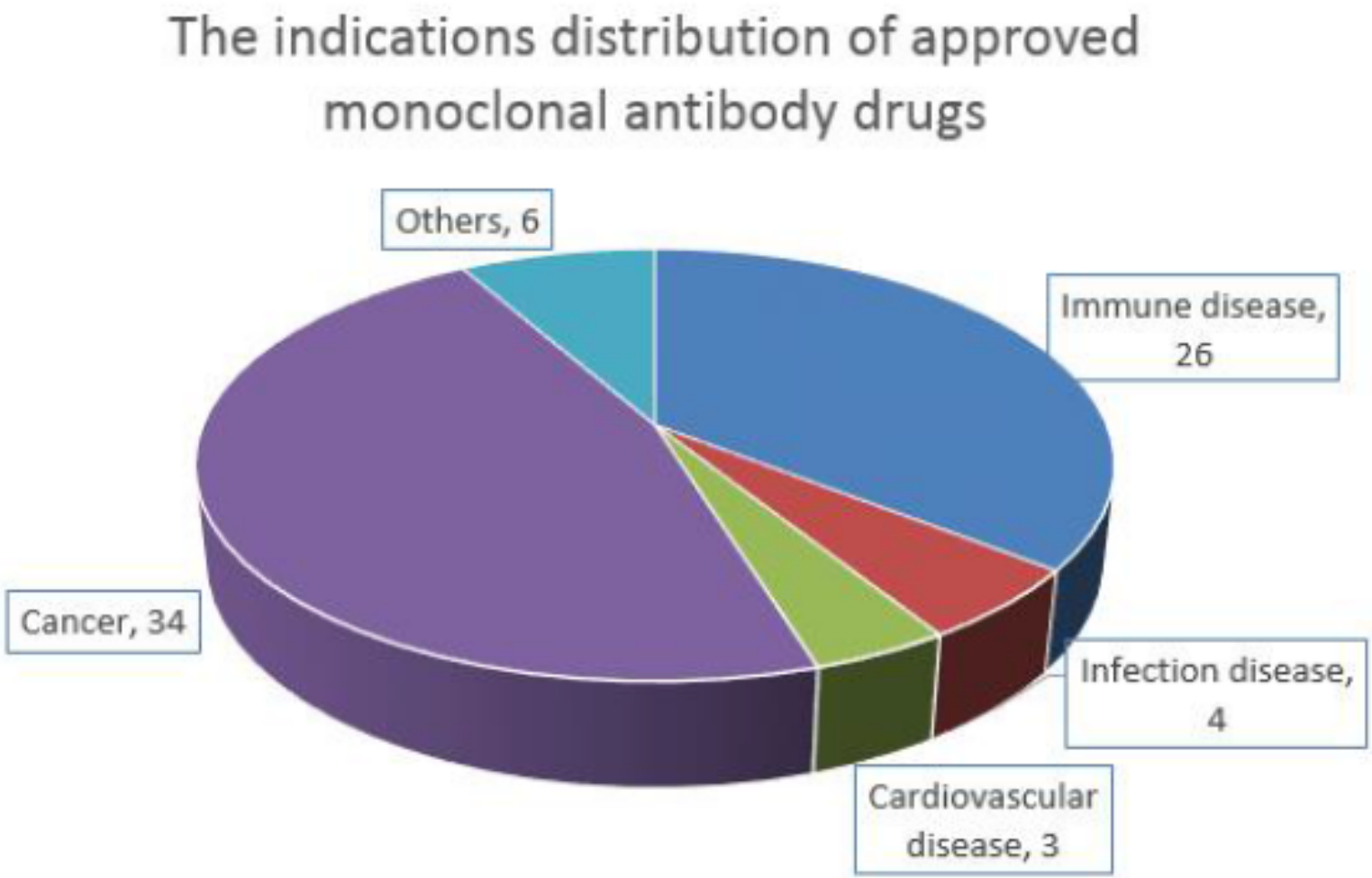
Negócios e parcerias | Hospital Vital Brazil | Recepção de animais | Calendário | fundação butantan Fundação de apoio | Sustentabilidade | Inovação | Primeiros socorros | Contatos

Imunobiológicos/Imunoterapêuticos - Brasil



Imunoterapias: perspectivas

Mabs: indicações



Site Criative Biologics

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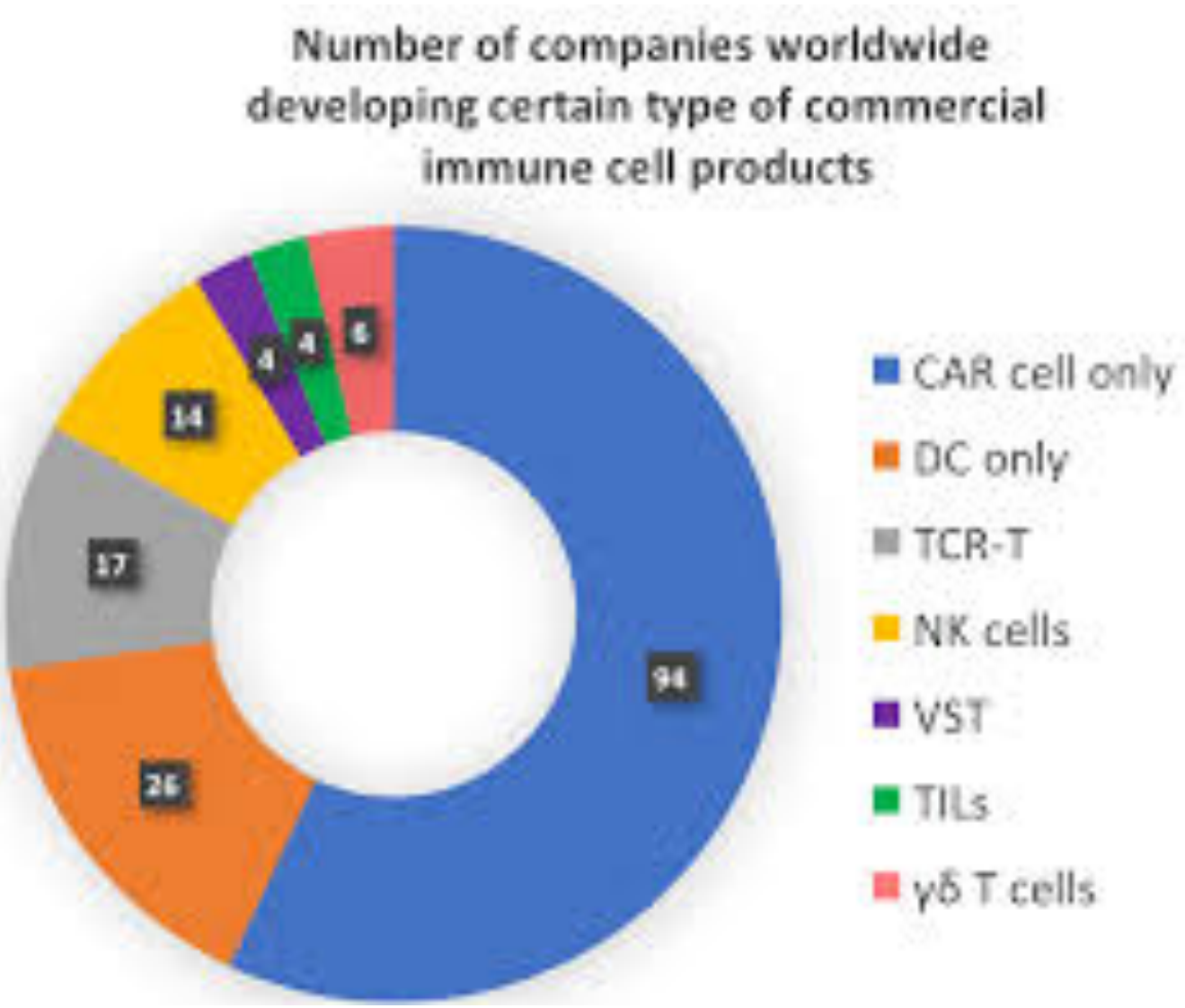

Combinação de imunoterapias e terapias-alvo no câncer

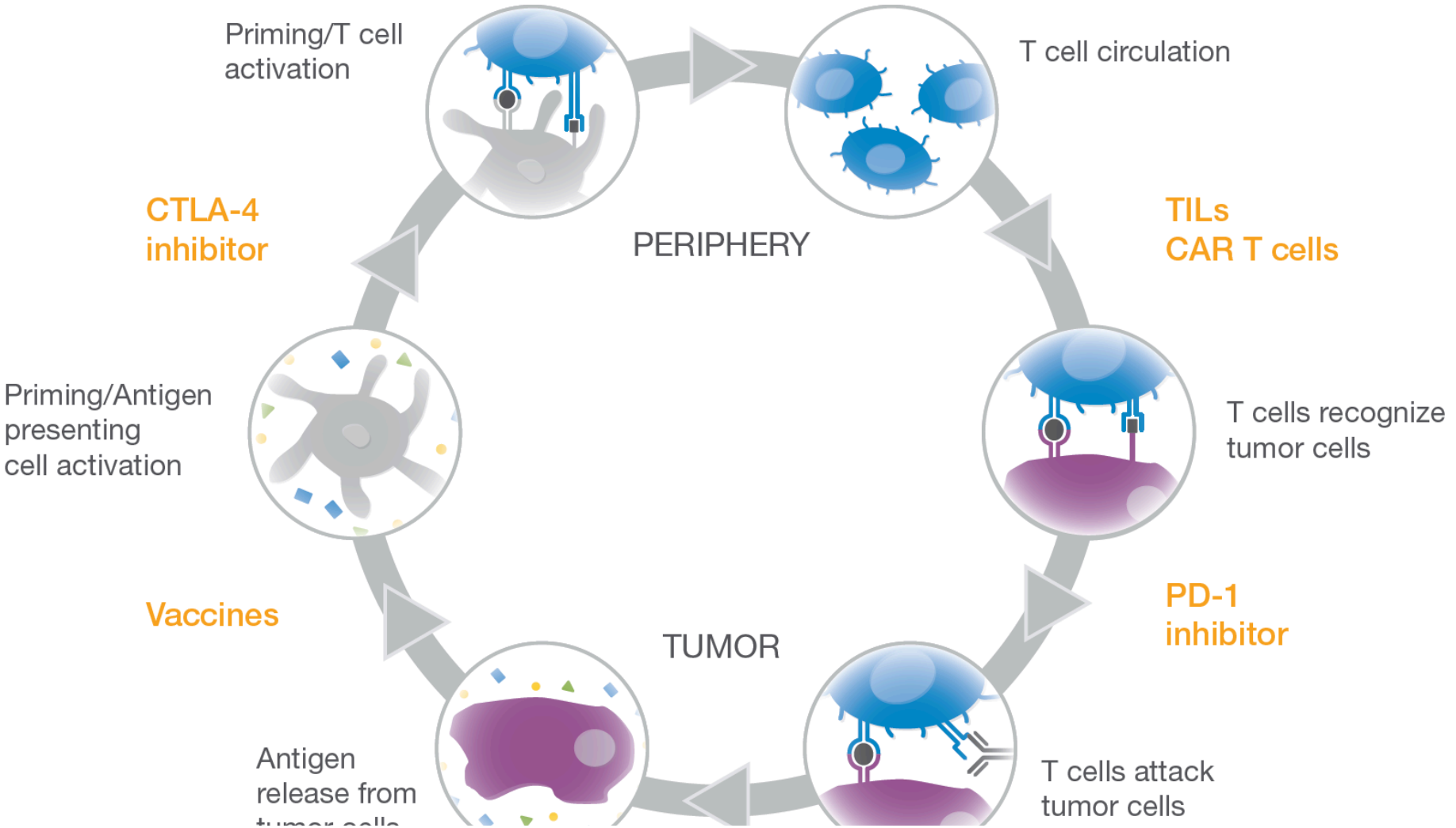

Figure 1: T Cell Mediated Immunity—Many steps are necessary for establishing a successful immune response, which may be augmented with immunotherapies.

CANCER

Hematopoietic stem cell transplantation in its 60s: A platform for cellular therapies

Christian Chabannon,[1]* Jurgen Kuball,[2] Attilio Bondanza,[3] Francesco Dazzi,[4] Paolo Pedrazzoli,[5] Antoine Toubert,[6] Annalisa Ruggeri,[7,8] Katharina Fleischhauer,[9] Chiara Bonini[10]*

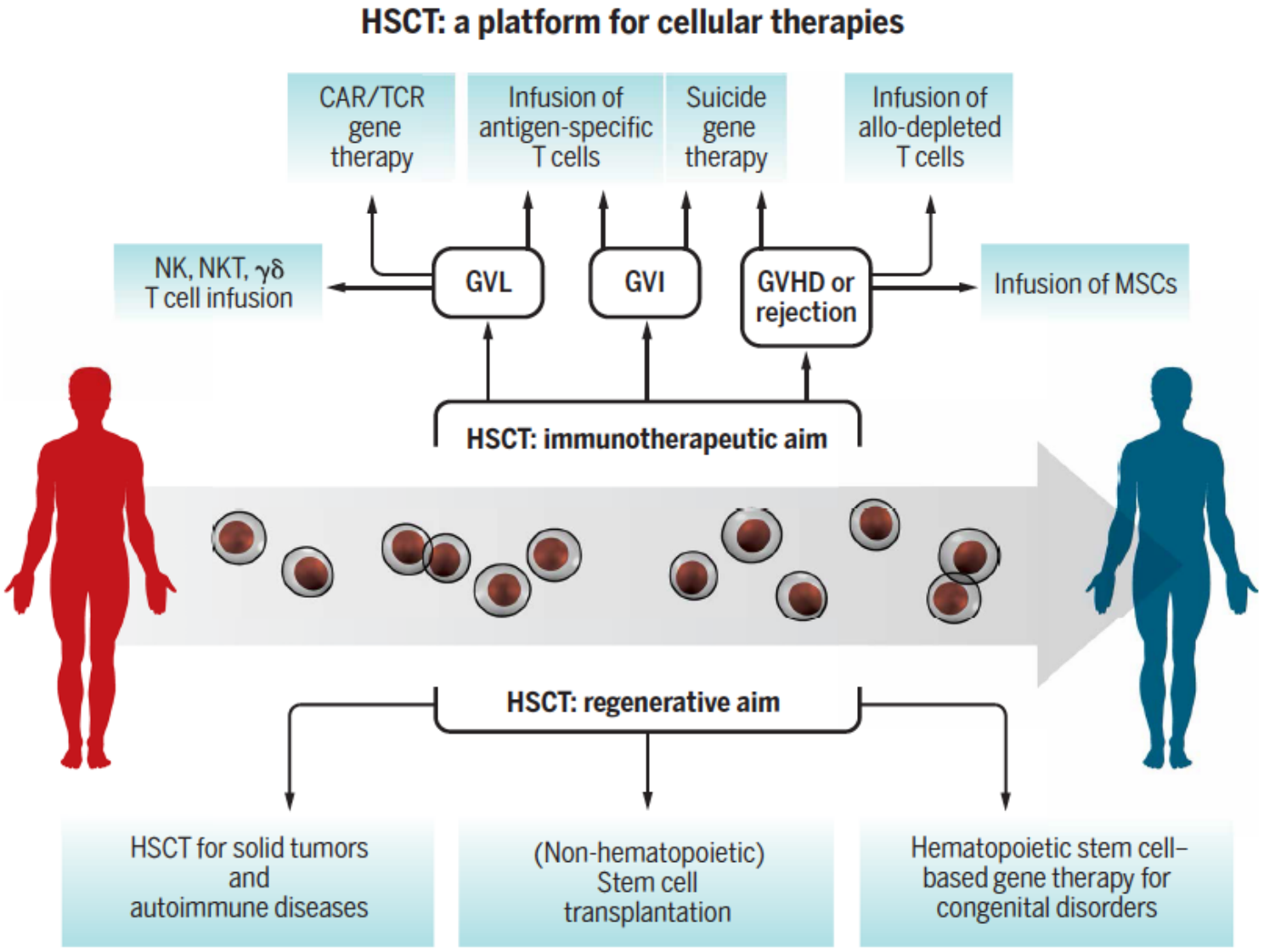

Fig. 1. HSCT: A platform for cellular therapies. The major biological determinants of clinical outcome after HSCT are the ability of HSCs to regenerate the host hemato-

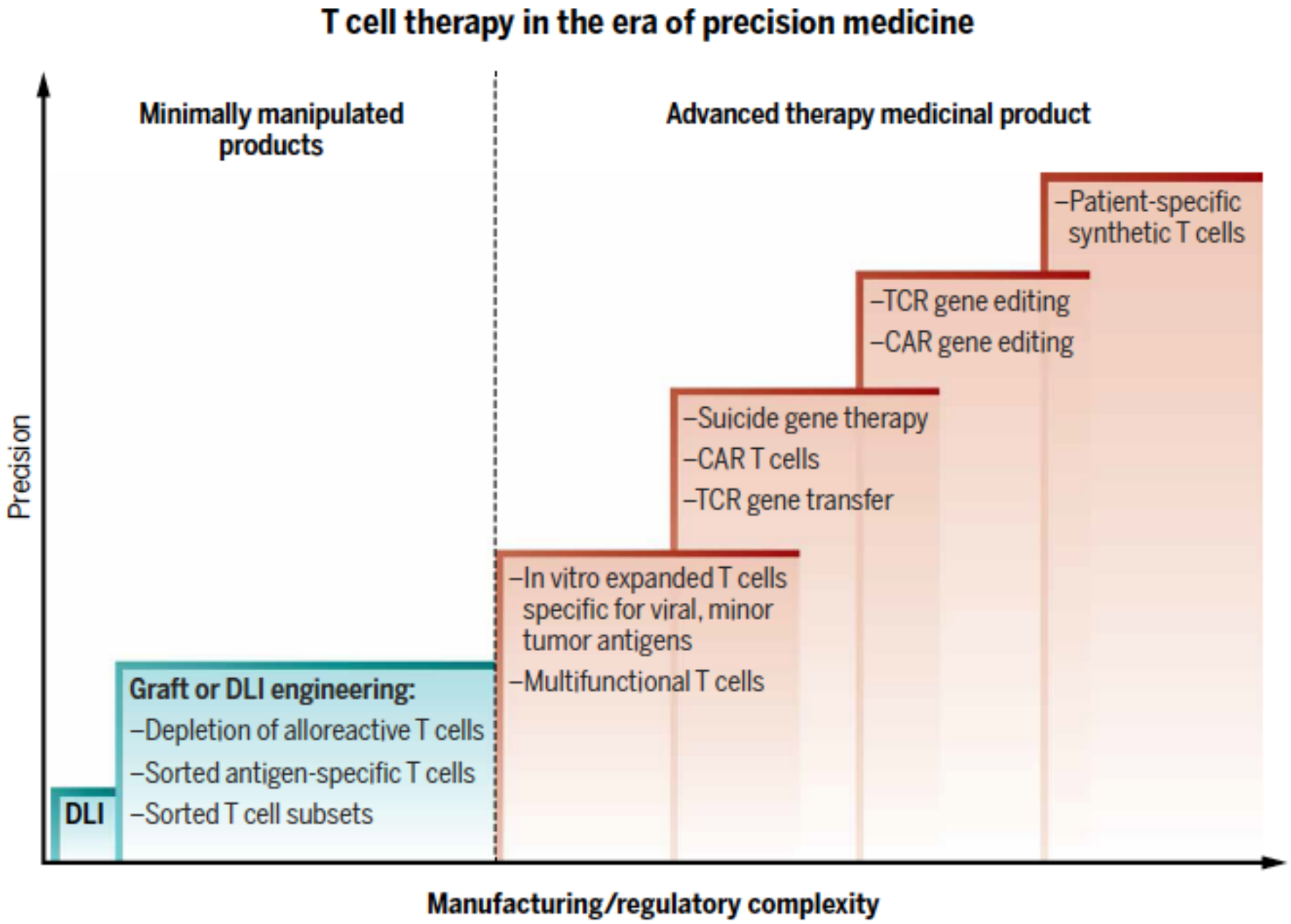

Fig. 4. T cell therapy in the era of precision medicine. Increased complexity in manufacturing costs and

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