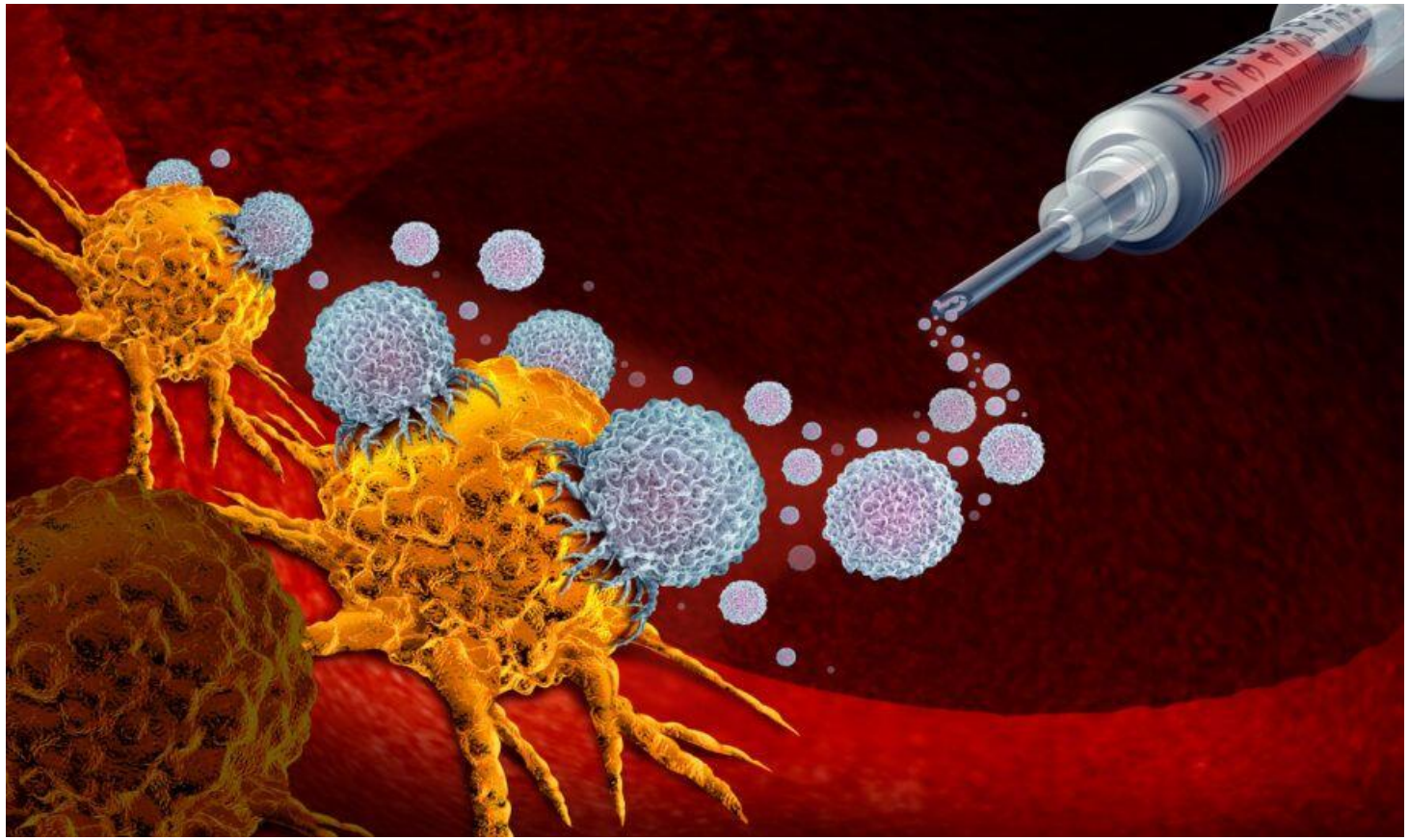
Imunoterapia

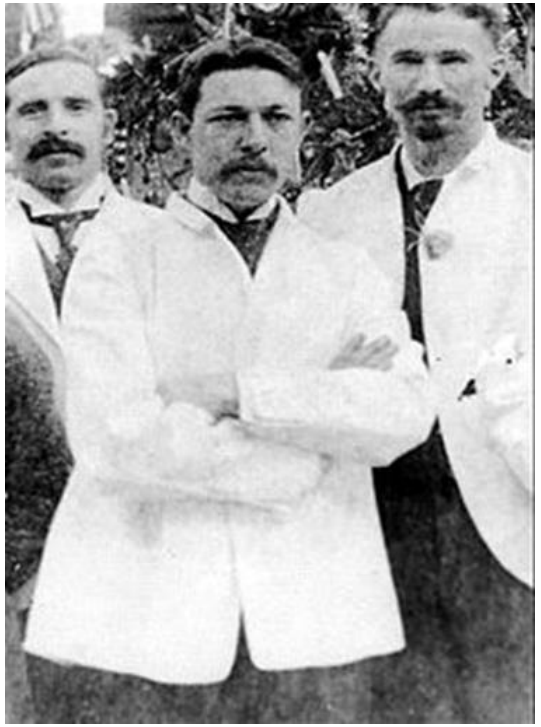


"We may one day be able to use immunotherapy to artificially induce equilibrium and convert cancer into a chronic but controllable disease."

Mark J. Smyth, Ph.D., professor of the Cancer Immunology Program at the Peter McCallum Cancer Centre in Melbourne, Australia

Empowering your immune system to fight

Introdução e Contexto Histórico



- Dr William Coley - “Father of Immuno-therapy,” – 1891

- Pacientes com diagnóstico de sarcoma que desenvolveram erisipela causada por *Streptococcus pyogenes*

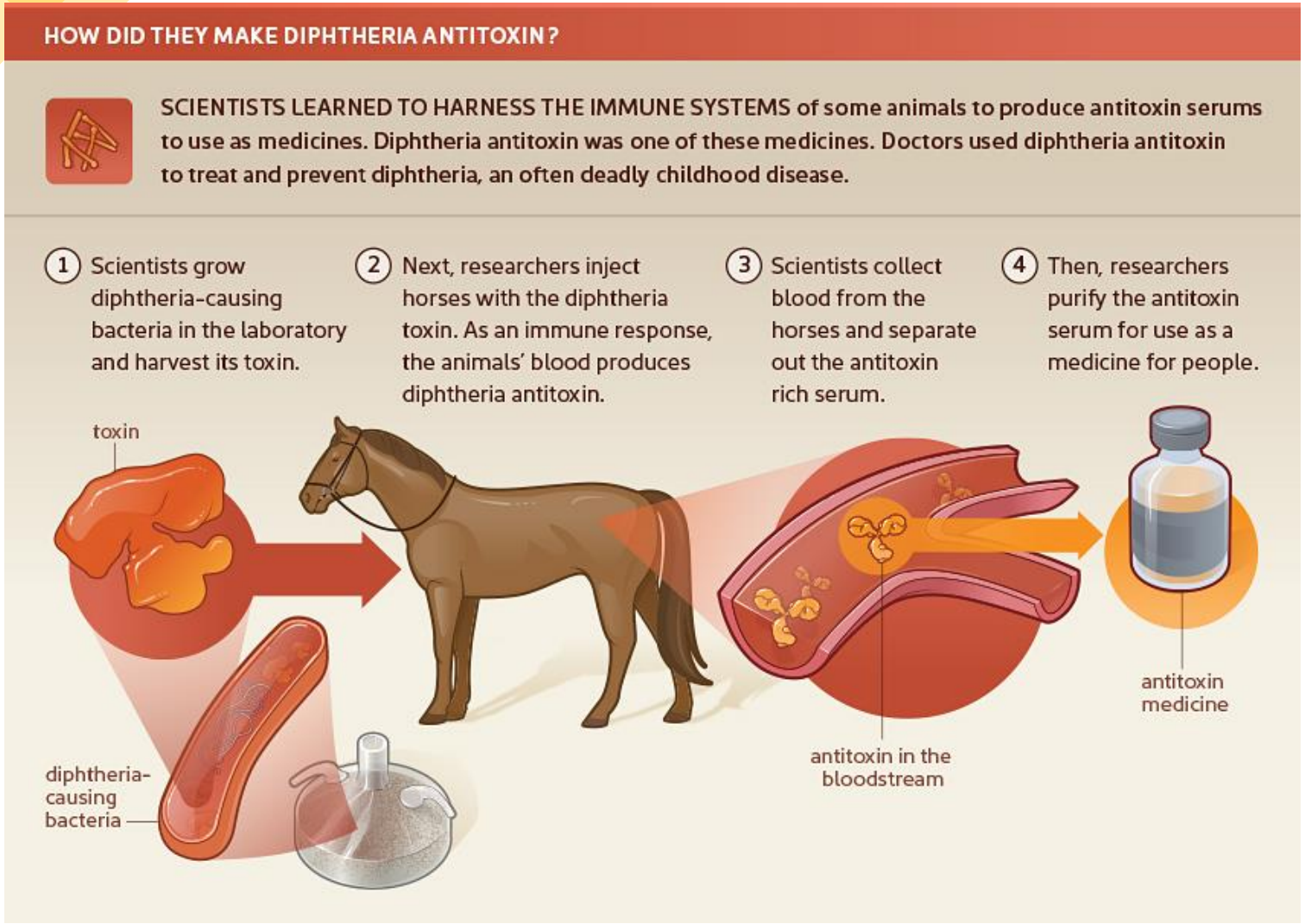
- Poderia uma infecção produzida intencionalmente estimular o sistema imunológico para tratar o câncer?

- “Toxina mista de Coley“: ele injetou bactérias nesses tumores e observou que esses sarcomas retrocederam, pois isso causou uma resposta imune levando a remissão completa e durável para pacientes com várias doenças malignas, incluindo sarcoma, linfoma e câncer testicular.

Abbott, M., & Ustoyev, Y. (2019, October). Cancer and the immune system: the history and background of immunotherapy. In *Seminars in oncology nursing* (Vol. 35, No. 5, p. 150923). WB Saunders.

Ginex, P. K., Brassil, K., & Ely, B. (2017). Immunotherapy: Exploring the state of the science. *Clinical journal of oncology nursing*, *21*.

Introdução e Contexto Histórico



- Emil von Behring e Shibasaburo Kitasato, em 1890, descobriram que a injeção de toxina diftérica em animais produz um soro contendo uma antitoxina que fornece imunidade antidifteria passiva às pessoas.

Emil Adolf von Behring
The Nobel Prize in Physiology or Medicine 1901

https://www.nobelprize.org/prizes/medicine/1901/behring/biographical/

Imunoterapias

A imunoterapia é definida como o uso de materiais para aumentar e/ou restabelecer a capacidade do sistema imunológico de prevenir e combater a doença.

- Cada imunoterapia visa melhorar a função imunológica e difere por vários mecanismos de ação pelos quais são categorizadas.

➢ Ativas x Passivas

- Ativas : A imunoterapia ativa é a estimulação direta de uma resposta imunológica, memória imunológica e resposta duradoura. As vacinas são um exemplo de imunoterapias ativas.
- Passivas: As imunoterapias passivas, que incluem anticorpos monoclonais, produzem respostas específicas, mas geralmente de curta duração, que, portanto, requerem a administração regular desses tratamentos.

Abbott, M., & Ustoyev, Y. (2019, October). Cancer and the immune system: the history and background of immunotherapy. In *Seminars in oncology nursing* (Vol. 35, No. 5, p. 150923). WB Saunders.

Soroterapia

https://butantan.gov.br/noticias/instituto-butantan-inicia-ensaios-clinicos-do-soro-anti-covid

Primeiro paciente recebe soro anti-Covid desenvolvido pelo Butantan

Material, produzido a partir do plasma de cavalos, não substitui a vacina, mas é uma possibilidade de tratamento para diagnosticados com a doença. Testes foram autorizados pela Anvisa no início de maio.

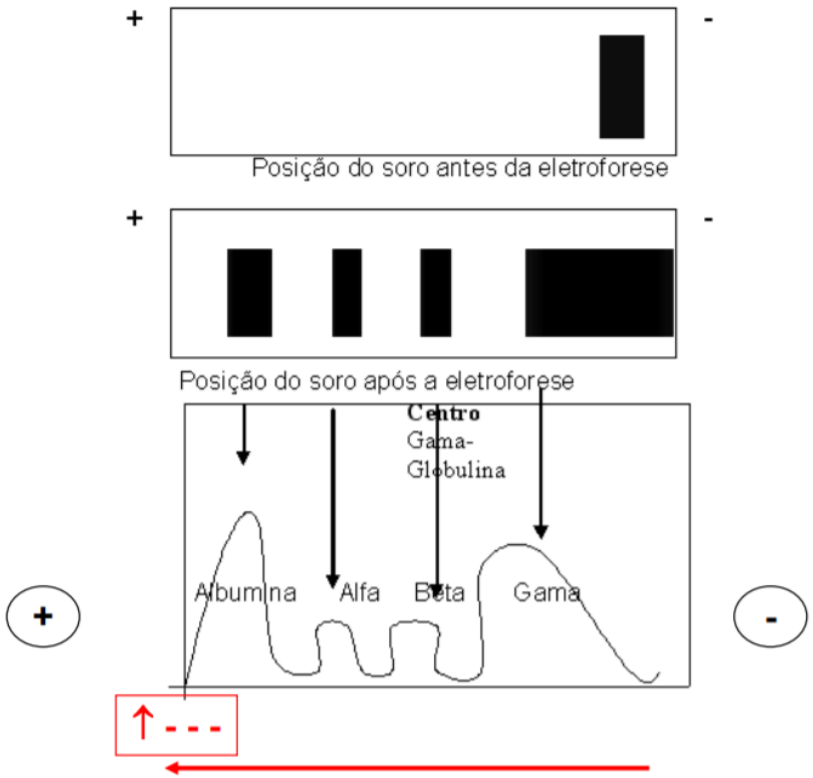
Por Amanda Lüder, GloboNews — São Paulo
16/11/2021 14h32 · Atualizado há 2 semanas

https://g1.globo.com/sp/sao-paulo/noticia/2021/11/16/primeiro-paciente-recebe-soro-anti-covid-desenvolvido-pelo-butantan.ghtml

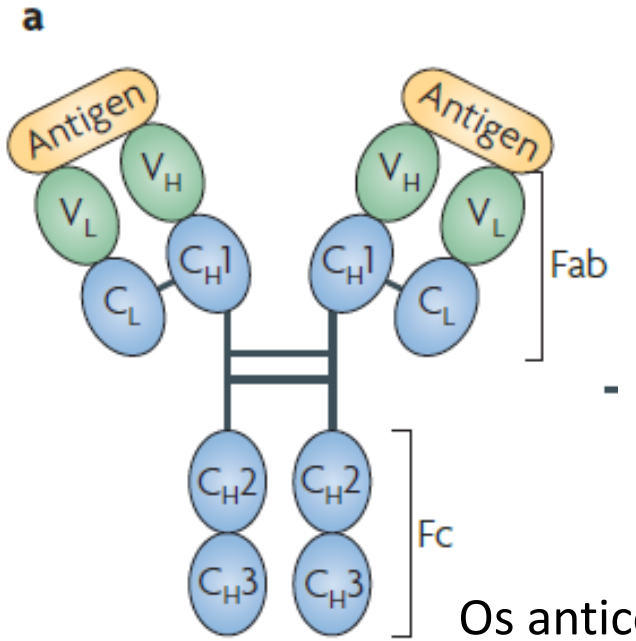
- Como um dos maiores produtores de soros da América Latina, o Butantan atua na produção de 13 tipos de soros, entre antiofídicos (contra veneno de cobra), antiescorpiônico (escorpião), antiaracnídico (aranhas e escorpião), antilonômico (lagarta), antidiftérico (difteria), antitetânico (tétano), antibotulínico (botulismo) e antirrábico (raiva), além de versões combinadas.
- https://www.youtube.com/watch?v=n0YAn-FvgTI
- Soro anti-Covid para pacientes imunossuprimidos.

Anticorpos Monoclonais

Técnica de Eletroforese:
Separação em meio liquido sob a influência de um campo elétrico.



Nas separações eletroforéticas de soro ou plasma, a maioria dos anticorpos é encontrada no terceiro grupo mais rápido de migração das globulinas, denominado **gamaglobulinas**



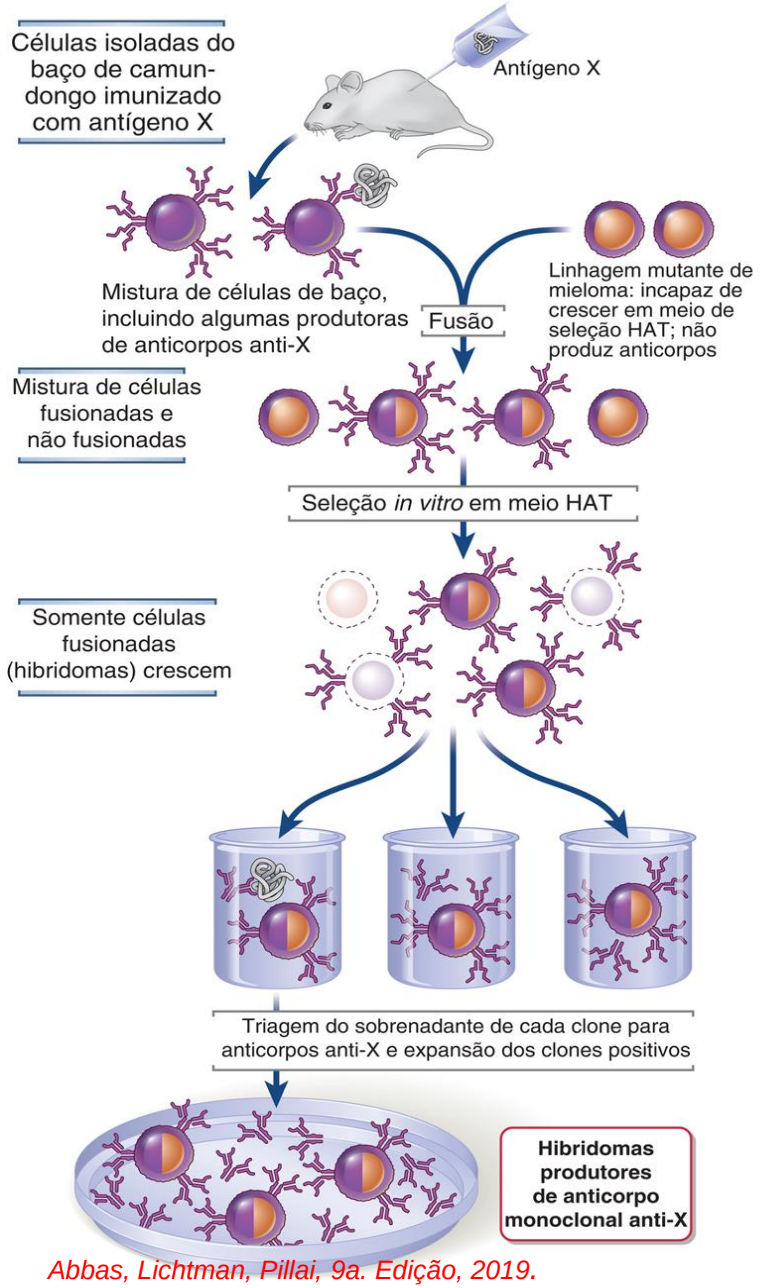
Região Fab – região de ligação ao antígeno
Região Fc - função efetora, cadeia pesada

Os anticorpos são sintetizados pela linhagem de linfócitos B

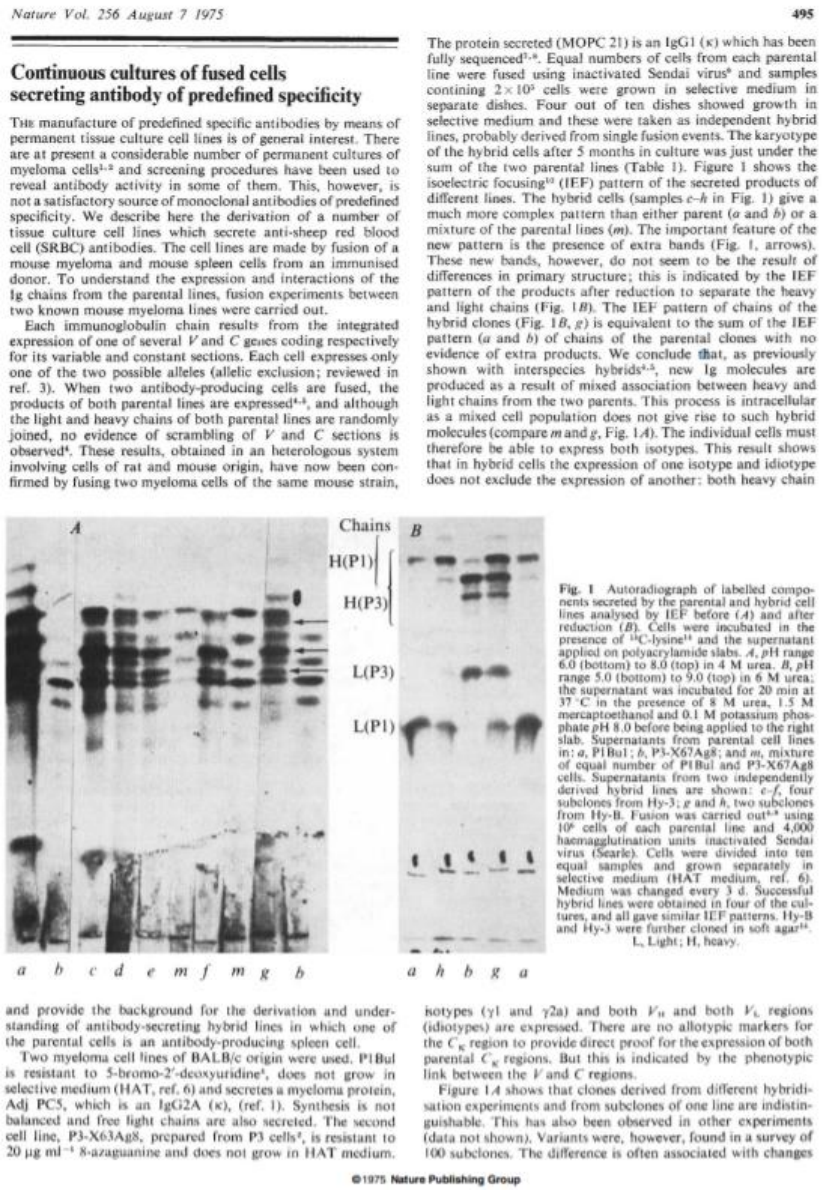
- Anticorpos ligados a membrana na superfície de linfócitos B
- Anticorpos secretados

https://www.fcav.unesp.br/Home/departamentos/patologia/HELIOJOSEMONTASSIER/aula-pratica-6--imunoeletroforese.pdf

Anticorpos Monoclonais



Abbas, Lichtman, Pillai, 9a. Edição, 2019.



Nature Vol. 256 August 7 1975 495

Continuous cultures of fused cells secreting antibody of predefined specificity

THE manufacture of predefined specific antibodies by means of permanent tissue culture cell lines is of general interest. There are at present a considerable number of permanent cultures of myeloma cells[1,2] and screening procedures have been used to reveal antibody activity in some of them. This, however, is not a satisfactory source of monoclonal antibodies of predefined specificity. We describe here the derivation of a number of tissue culture cell lines which secrete anti-sheep red blood cell (SRBC) antibodies. The cell lines are made by fusion of a mouse myeloma and mouse spleen cells from an immunised donor. To understand the expression and interactions of the Ig chains from the parental lines, fusion experiments between two known mouse myeloma lines were carried out.

Each immunoglobulin chain results from the integrated expression of one of several *V* and *C* genes coding respectively for its variable and constant sections. Each cell expresses only one of the two possible alleles (allelic exclusion; reviewed in ref. 3). When two antibody-producing cells are fused, the products of both parental lines are expressed[4-6], and although the light and heavy chains of both parental lines are randomly joined, no evidence of scrambling of *V* and *C* sections is observed[4]. These results, obtained in an heterologous system involving cells of rat and mouse origin, have now been confirmed by fusing two myeloma cells of the same mouse strain, and provide the background for the derivation and understanding of antibody-secreting hybrid lines in which one of the parental cells is an antibody-producing spleen cell.

Two myeloma cell lines of BALB/c origin were used. P1Bul is resistant to 5-bromo-2′-deoxyuridine[4], does not grow in selective medium (HAT, ref. 6) and secretes a myeloma protein, Adj PC5, which is an IgG2A (κ), (ref. 1). Synthesis is not balanced and free light chains are also secreted. The second cell line, P3-X63Ag8, prepared from P3 cells[7], is resistant to 20 μg ml^{-1} 8-azaguanine and does not grow in HAT medium. The protein secreted (MOPC 21) is an IgG1 (κ) which has been fully sequenced[7-9]. Equal numbers of cells from each parental line were fused using inactivated Sendai virus[8] and samples containing 2×10^5 cells were grown in selective medium in separate dishes. Four out of ten dishes showed growth in selective medium and these were taken as independent hybrid lines, probably derived from single fusion events. The karyotype of the hybrid cells after 5 months in culture was just under the sum of the two parental lines (Table 1). Figure 1 shows the isoelectric focusing[10] (IEF) pattern of the secreted products of different lines. The hybrid cells (samples *c–h* in Fig. 1) give a much more complex pattern than either parent (*a* and *b*) or a mixture of the parental lines (*m*). The important feature of the new pattern is the presence of extra bands (Fig. 1, arrows). These new bands, however, do not seem to be the result of differences in primary structure; this is indicated by the IEF pattern of the products after reduction to separate the heavy and light chains (Fig. 1*B*). The IEF pattern of chains of the hybrid clones (Fig. 1*B*, *g*) is equivalent to the sum of the IEF pattern (*a* and *b*) of chains of the parental clones with no evidence of extra products. We conclude that, as previously shown with interspecies hybrids[4,5], new Ig molecules are produced as a result of mixed association between heavy and light chains from the two parents. This process is intracellular as a mixed cell population does not give rise to such hybrid molecules (compare *m* and *g*, Fig. 1*A*). The individual cells must therefore be able to express both isotypes. This result shows that in hybrid cells the expression of one isotype and idiotype does not exclude the expression of another: both heavy chain isotypes (γ1 and γ2a) and both V_H and both V_L regions (idiotypes) are expressed. There are no allotypic markers for the C_K region to provide direct proof for the expression of both parental C_K regions. But this is indicated by the phenotypic link between the *V* and *C* regions.

Figure 1*A* shows that clones derived from different hybridisation experiments and from subclones of one line are indistinguishable. This has also been observed in other experiments (data not shown). Variants were, however, found in a survey of 100 subclones. The difference is often associated with changes

Fig. 1 Autoradiograph of labelled components secreted by the parental and hybrid cell lines analysed by IEF before (*A*) and after reduction (*B*). Cells were incubated in the presence of ^{14}C-lysine[11] and the supernatant applied on polyacrylamide slabs. *A*, pH range 6.0 (bottom) to 8.0 (top) in 4 M urea. *B*, pH range 5.0 (bottom) to 9.0 (top) in 6 M urea; the supernatant was incubated for 20 min at 37 °C in the presence of 8 M urea, 1.5 M mercaptoethanol and 0.1 M potassium phosphate pH 8.0 before being applied to the right slab. Supernatants from parental cell lines in: *a*, P1Bul; *b*, P3-X67Ag8; and *m*, mixture of equal number of P1Bul and P3-X67Ag8 cells. Supernatants from two independently derived hybrid lines are shown: *c–f*, four subclones from Hy-3; *g* and *h*, two subclones from Hy-B. Fusion was carried out[4,5] using 10^6 cells of each parental line and 4,000 haemagglutination units inactivated Sendai virus (Searle). Cells were divided into ten equal samples and grown separately in selective medium (HAT medium, ref. 6). Medium was changed every 3 d. Successful hybrid lines were obtained in four of the cultures, and all gave similar IEF patterns. Hy-B and Hy-3 were further cloned in soft agar[12]. L, Light; H, heavy.

The Nobel Prize in Physiology or Medicine 1984

Fig. 1. A port trait of César Milstein.

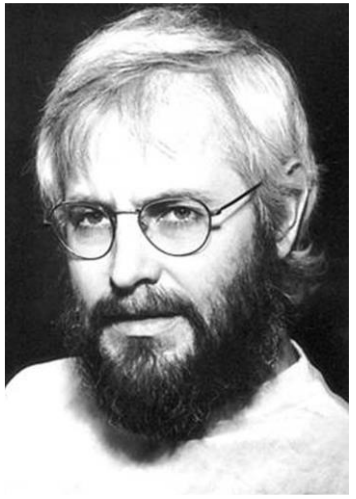


Fig. 2. A port trait of Georges Köhler.

Ribatti, D. (2014). From the discovery of monoclonal antibodies to their therapeutic application: An historical reappraisal. *Immunology letters*, *161*(1), 96-99.

Anticorpos Monoclonais

Monoclonal antibodies approved for the treatment of transplant rejection and auto-immune diseases.

Transplant Rejection					
Sr. No	**Name**	**Target**	**Type**	**Use**	**Year**
1	Muromonab	CD_3	Murine	Acute graft versus host disease	1992
2	Basiliximab	IL-2 receptor antago-nist	Chimeric	Prophylaxis of renal transplant rejection	1998
MAB* with their targets: Cedelizumab (CD4), Gavilimomab (CD147), Inolimomab (CD25), Odulimomab (CD11a), Siplizumab (CD2), Teneliximab (CD40), Zolimomabaritox (CD5). **Abbreviations used:** CD: Cluster of Differentiation, IL: Interleukin.					
Autoimmune Disease (Skin, GIT, Bone & Joint, CNS & Nerve)					
1	Infliximab	TNF alpha	Chimeric	Rheumatoid arthritis (RA), Psoriatic arthritis (PA), Ankylosing spondylitis (AS), Ulcerative colitis (UC), Crohn's disease (CD), Plaque psoriasis	1998
2	Adalimumab	TNF alpha	Human	RA, PA, AS, CD, UC	2002
3	Ustekinumab	IL-12 & 23	Human	Plaque Psoriasis, PA, CD	2009
4	Secukinumab	IL-17A	Human	Psoriasis, PA, AS	2015
5	Brodalumab	IL-17	Human	Plaque Psoriasis, PA	2016
6	Efalizumab	LFA-1 (CD11a)	Humanized	Plaque Psoriasis	2003
7	Vedolizumab	Integrin alpha 4 beta 7	Humanized	CD, UC	2014
8	Canakinumab	IL-1 beta	Human	Cryoporin associated periodic syndrome, TNF receptor associated periodic syndrome, Hyperimmunoglobulin D syndrome, Familial mediterranean syndrome	2009
9	Denosumab	RANKL	Human	Osteoporosis, Aromatase inhibitor induced bone loss, Androgen deprivation induced bone loss, Giant cell tumor, Hypercalcemia of malignancy, Skeletal related events (Bone fracture & pain)	2009
10	Golimumab	TNF alpha	Human	RA, PA, AS, UC	2009
11	Tocilizumab	IL-6 receptor	Human	RA	2010
12	CertolizumabPegol	TNF alpha	Humanized	CD	2008
13	Belimumab	BAFF	Human	Systemic Lupus Erythrematous (SLE)	2011
14	Ixekizumab	IL-17A	Humanized	Psoriasis	2016
15	Rituximab	CD20	Chimeric	RA, CLL, NHL, Wegner's granulomatosis, microscopic polyangi-tis	1997
16	Daclizumab	IL-2 receptor subunit CD_{25}	Humanized	Multiple sclerosis (MS)	1997
17	Alemtuzumab	CD52	Humanized	MS, CLL	2001
18	Natalizumab	Alpha 4 subunit	Humanized	MS, CD	2004

Singh, S., Tank, N. K., Dwiwedi, P., Charan, J., Kaur, R., Sidhu, P., & Chugh, V. K. (2018). Monoclonal antibodies: a review. *Current clinical pharmacology*, *13*(2), 85-99.

Anticorpos Monoclonais

Monoclonal antibodies approved for the treatment of malignancy.

				Malignancy	
1	Trastuzumab	HER-2 protein	Humanized	Breast cancer, Gastric cancer	1998
2	Trastuzumab Emtansine	HER-2/neu	Humanized	Breast cancer, Gastric cancer	2013
3	Ibritumomab tituxetan	CD 20	Murine	Non hodgkin lymphoma (NHL)	2002
4	Tositumomab	CD 20	Murine	NHL	2003
5	Cetuximab	EGFR inhibitor	Chimeric	Colorectal carcinoma, Head & neck cancer	2004
6	Panitumumab	EGFR inhibitor	Human	Colorectal carcinoma	2007
7	Dinutuximab	GD2 gangloside	Chimeric	Neuroblatoma (in children)	2015
8	Ipilimumab	CTLA4	Human	Malignant melanoma	2011
9	Necitumumab	EGFR inhibitor	Human	Non small cell lung cancer (NSCLC)	2015
10	Ramucirumab	VEGFR2 antagonist	Human	NSCLC, Gastric cancer, Colorectal cancer	2014
11	Daratumumab	CD38	Human	Multiple myeloma	2015
12	Nivolumab	Programmed cell death-1 protein	Human	Melanoma, NSCLC, Head & neck squamous cell carcinoma, Renal cell cancer, Hodgkin lymphoma	2014
13	Pembrolizumab	Programmed cell death-1 protein	Humanized	Melanoma, NSCLC, Head & neck squamous cell carcinoma	2014
14	Gemtuzumab Ozogamicin	CD33	Humanized	Acute myeloid leukemia (AML)	2000
15	Ofatumumab	CD20	Human	Chronic lymphocytic leukemia (CLL)	2009
16	Brentuximab vedotin	CD 30	Chimeric	Hodgkin lymphoma, Systemic anaplastic large cell lymphoma	2011
17	Obinutuzumab	CD20	Humanized	Chronic myeloid leukemia, Follicular lymphoma	2013
18	Blinatumomab	CD19	Bispecific	Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia	2014
19	Elotuzumab	SLAMF7	Humanized	Multiple myeloma	2015
20	Olaratumab	PDGF R alpha	Human	Soft tissue sarcoma	2016
21	Pertuzumab	HER-2 protein	Humanized	Metastatic breast cancer, Neoadjuvant treatment of breast cancer	2012
22	Bevacizumab	VEGF	Humanized	Metastaic colorectal carcinoma, NSCLC, Breast cancer, Renal cell, Cervical, ovarian, Fallopian tube or Peritoneal cancer	2004
23	Avelumab	Programmed death ligand 1	Human	Metastatic Merkle cell carcinoma	2017

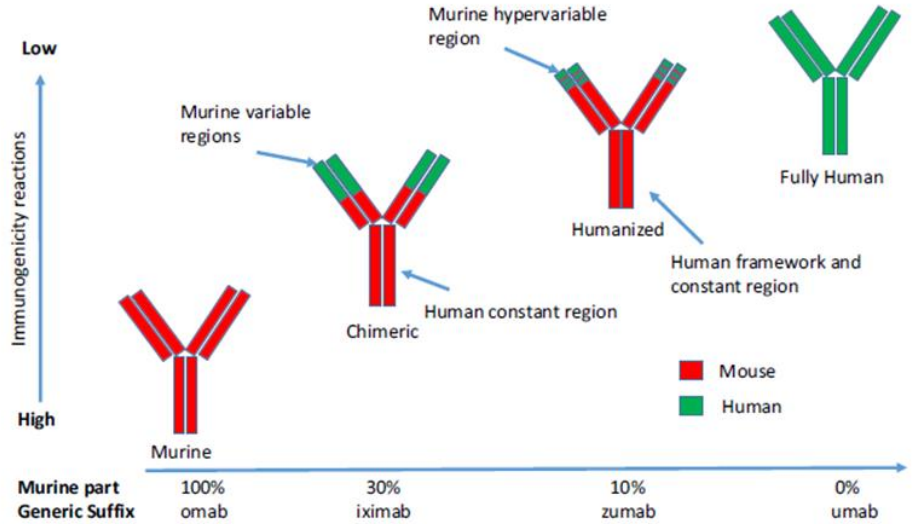
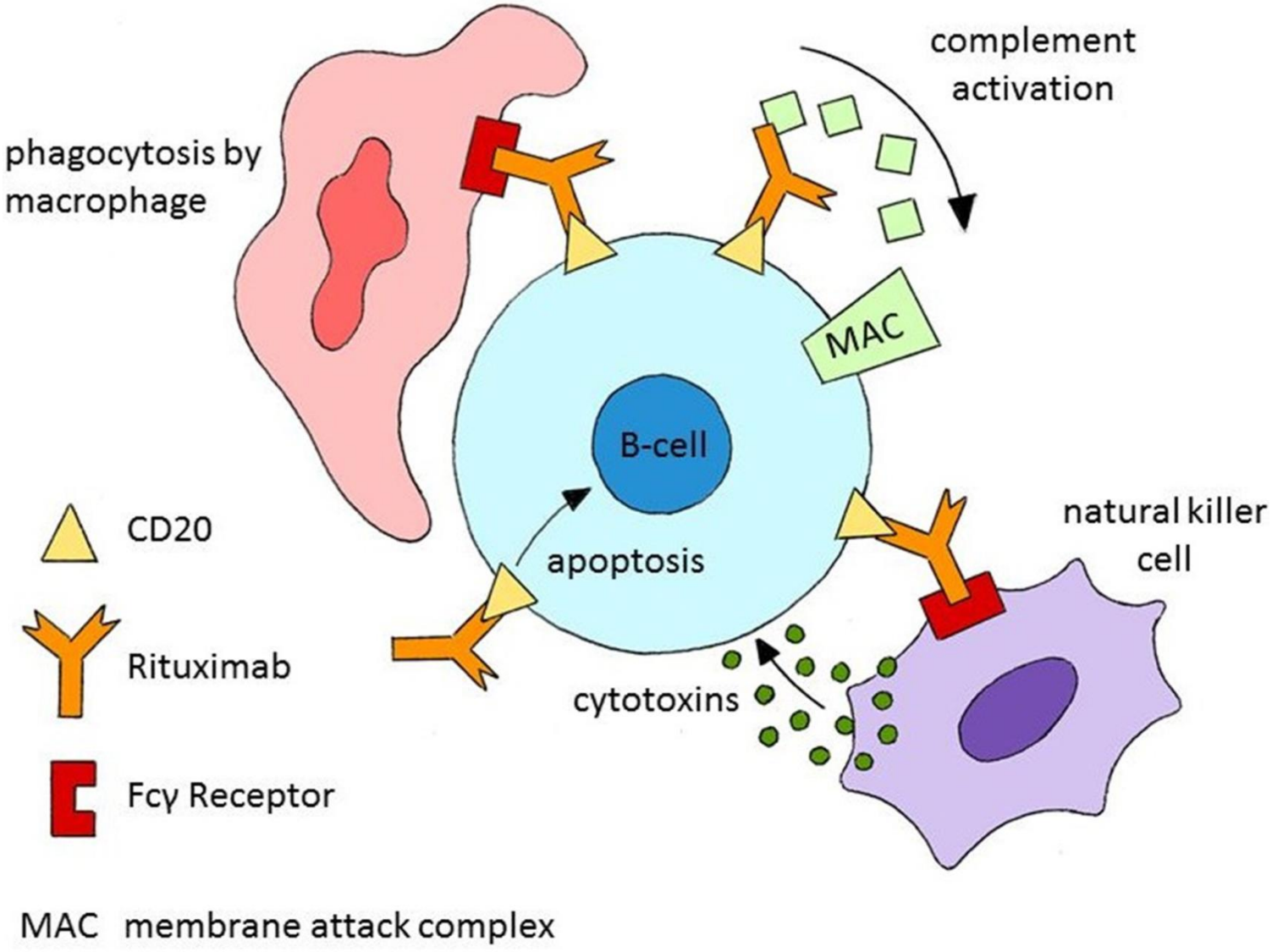


Fig. (1). Humanization of monoclonal antibodies.

Singh, S., Tank, N. K., Dwiwedi, P., Charan, J., Kaur, R., Sidhu, P., & Chugh, V. K. (2018). Monoclonal antibodies: a review. *Current clinical pharmacology*, *13*(2), 85-99.

Rituximab

Rituximab – Mecanismos de ação



Salles, G., Barrett, M., Foà, R., Maurer, J., O'Brien, S., Valente, N., ... & Maloney, D. G. (2017). Rituximab in B-cell hematologic malignancies: a review of 20 years of clinical experience. *Advances in therapy*, *34*(10), 2232-2273.

Anticorpos aprovados em 2020

Table 2: Some characteristics of the therapeutic Mab approved by FDA in 2020

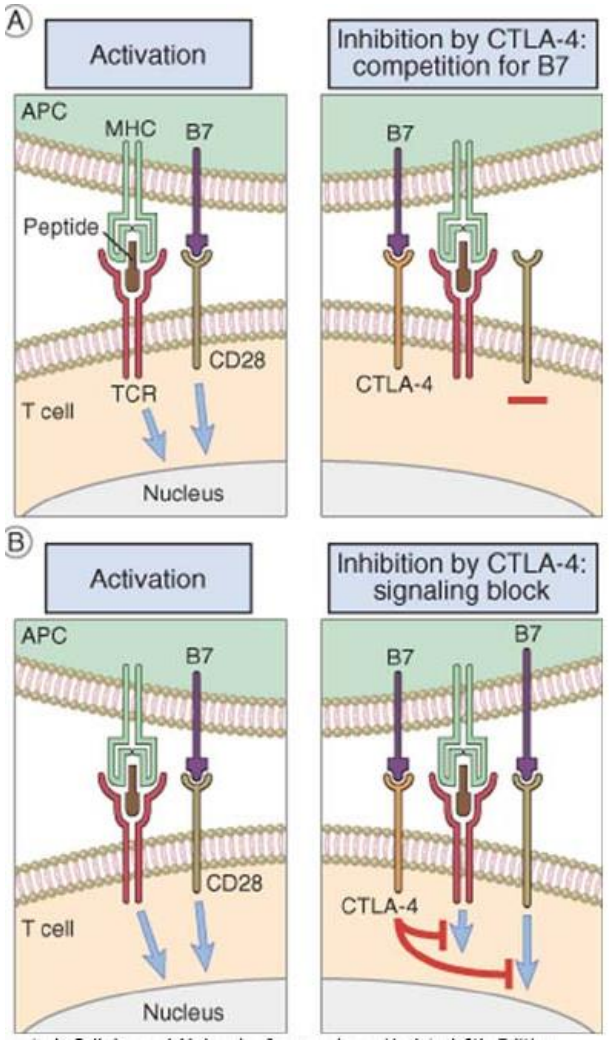
Drug name	Indications and usage	Warnings and precautions	Mechanism of action
TEPEZZ	Thyroid eye disease	IBD worsening; hyperglycemia	IGF-1R block
VYEPTI	Migraine	Hypersensitivity	CGRP block
SARCLISA	Multiple myeloma	Neutropenia; SPM	Anti-CD38, ADCC, CDC,
TRODELVY	mTNBC	Hypersensitivity, neutropenia	Anti-Trop-2; SN-38; ADC
DARZALEX FASPRO	Multiple myeloma	Hypersensitivity, Neutropenia	Anti-CD38, ADCC, CDC,
UPLIZNA	NMOSD (AQP4+)	Immune compromise	Anti-CD19
PHESGO	Breast cancer (HER2+)	Neutropenia	Anti-HER2; increases permeability
BLENREP	Multiple Myeloma	Thrombocytopenia	Anti-BCMA; microtubule inhibitor; ADC
ENSPRYNG	NMOSD (AQP4+)	Elevated liver enzymes	Anti-IL6 receptor
INMAZEB	Zaire ebolavirus infection.	Hypersensitivity	Zaire ebolavirus glycoprotein
DANYELZA	Neuroblastoma	Neurotoxicity; Hypertension	Anti-glycolipid GD2, CDC, ADCC
MARGENZA	Breast cancer	Left ventricular dysfunction	Anti-HER2, ADCC
RIABNI	NHL, CLL, GPA, MPA	IRR; TLS; PML	Anti-CD20, ADCC, CDC

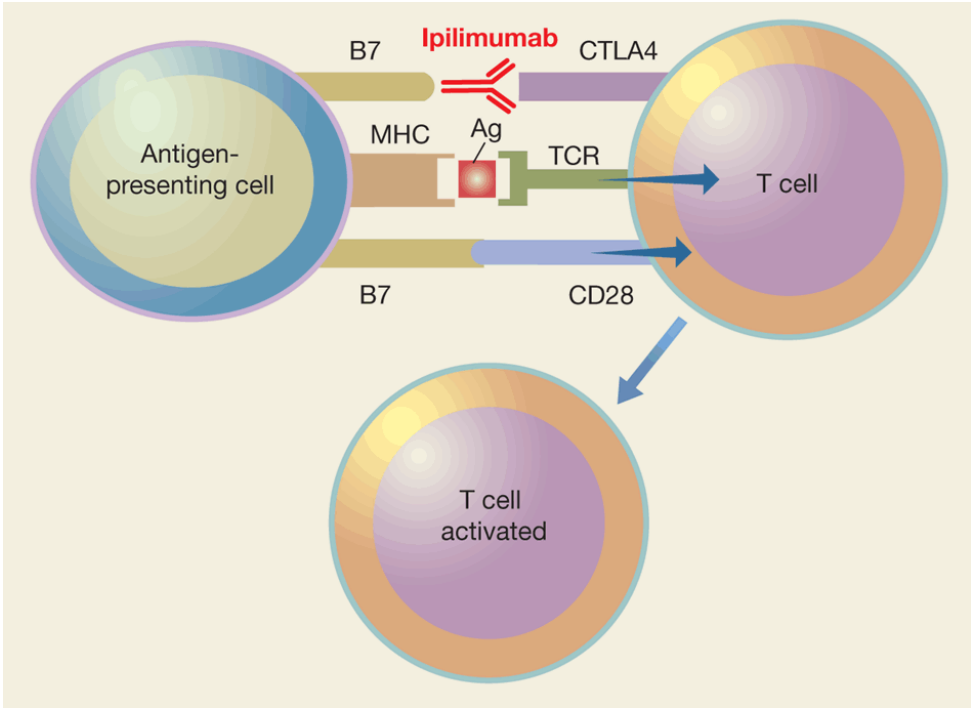
IBD: Inflammatory bowel disease, IGF-1R: Insulin-like growth factor 1 (IGF-1) receptor, CGRP: Calcitonin gene-related peptide, SPM: Second primary malignancies, ADCC: Antibody-dependent cell-mediated cytotoxicity, CDC: Complement-dependent cytotoxicity, ADCP: Antibody-dependent cellular phagocytosis, mTNBC: Metastatic triple-negative breast cancer, SN-38: Topoisomerase I inhibitor, ADC: Antibody drug conjugate, NMOSD: Neuromyelitis optica spectrum disorder, AQP4+: Anti-aquaporin-4 antibody positive, NHL: Non-Hodgkin's lymphoma, CLL: Chronic lymphocytic leukemia, GPA: Granulomatosis with polyangiitis (Wegener's granulomatosis), MPA: Microscopic polyangiitis, IRR: Infusion-related reaction, TLS: Tumor lysis syndrome, PML: Progressive multifocal leukoencephalopathy

Cai HH. Therapeutic Monoclonal Antibodies Approved by FDA in 2020. Clin Res Immunol 2021;4(1):1-2.

Anticorpos inibidores dos pontos de controle

CTLA-4 - Cytotoxic T Lymphocyte Associated Protein 4

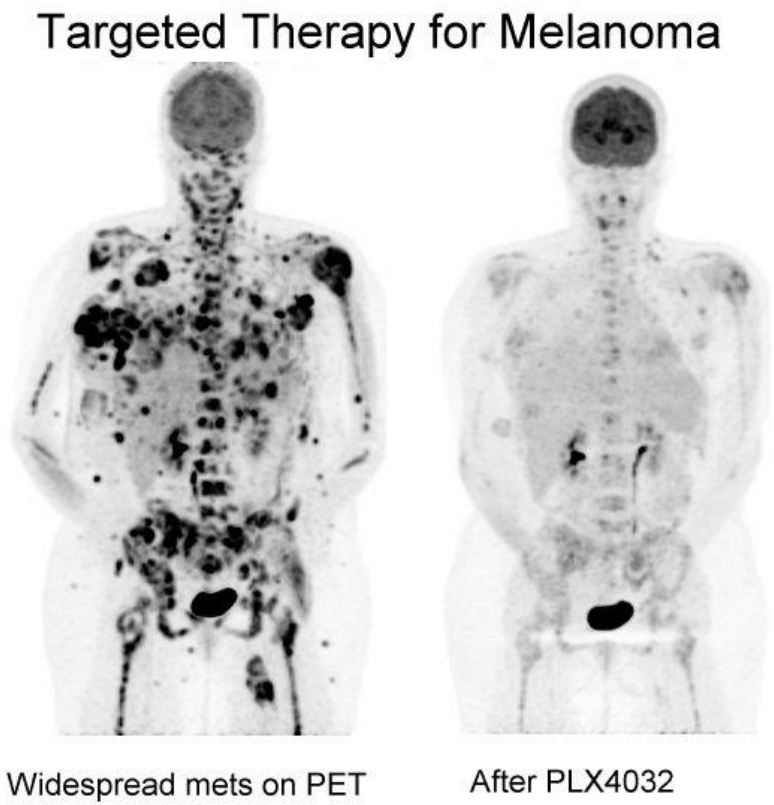


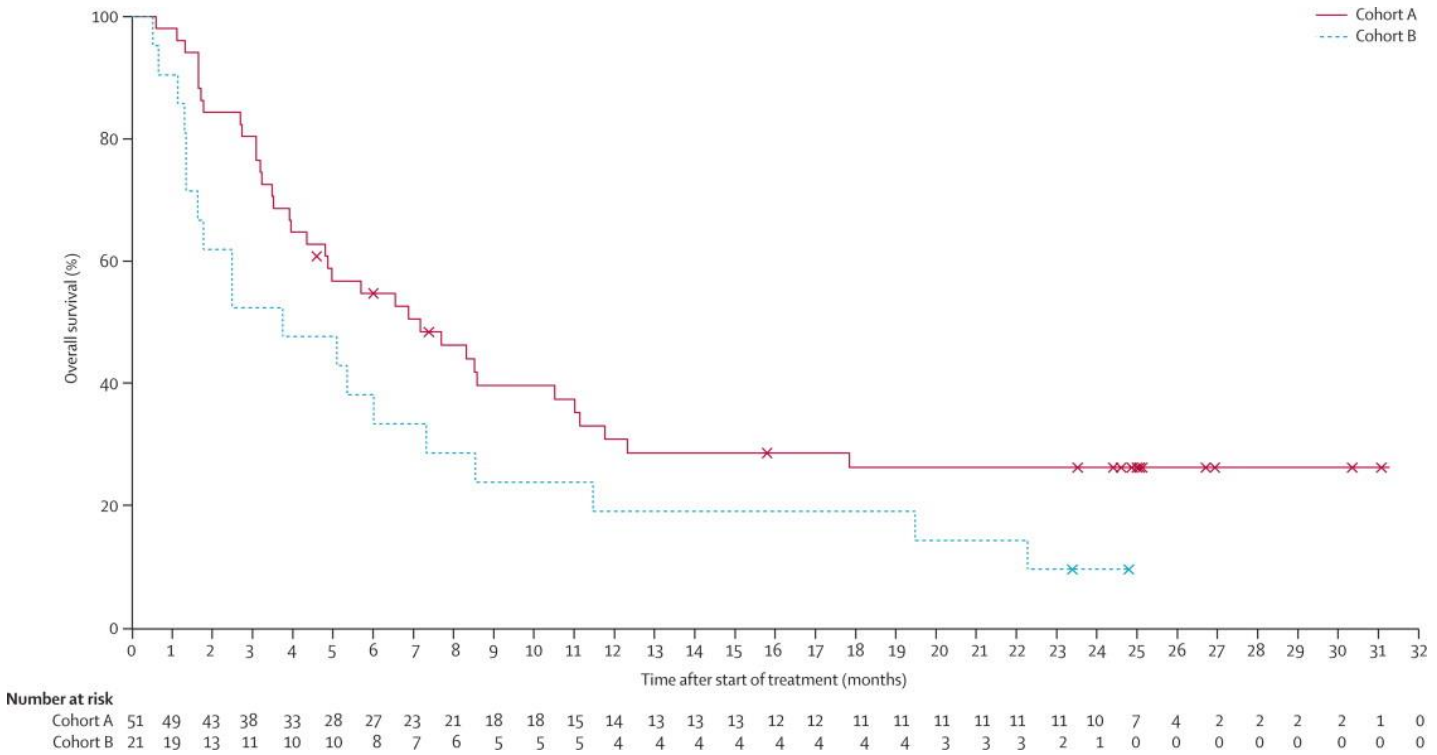


Abbas, Lichtman, Pillai, 9a. Edição, 2019.

Anticorpos inibidores dos pontos de controle

IMPILIMUMAB (ANTI-CTLA-4)





THE LANCET Oncology

Margolin, K., Ernstoff, M. S., Hamid, O., Lawrence, D., McDermott, D., Puzanov, I., ... & Hodi, F. S. (2012). Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial. *The lancet oncology*, *13*(5), 459-465.

Anticorpos inibidores dos pontos de controle

Morte celular programada 1 / ligante de morte celular programada 1 (PD1 / PDL1)

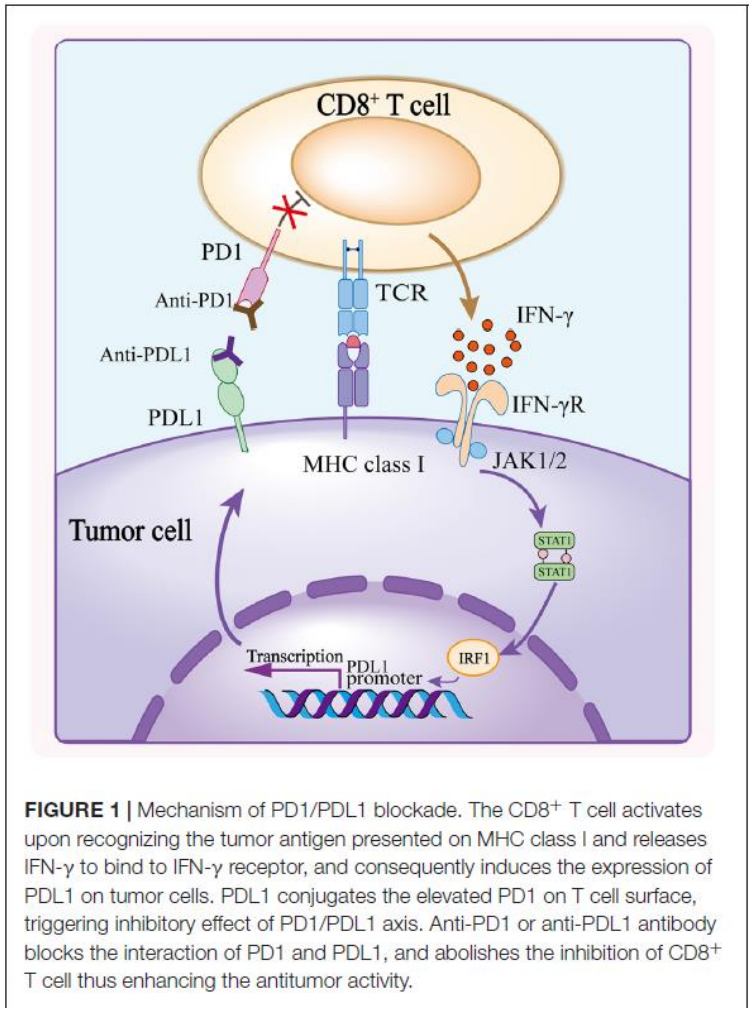
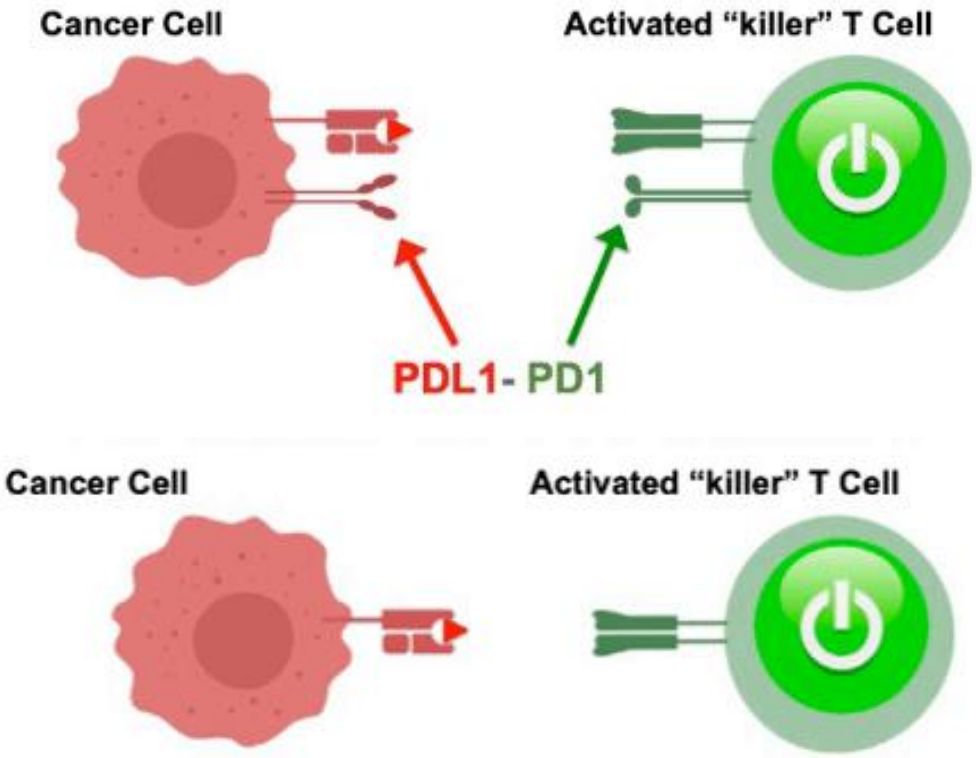


FIGURE 1 | Mechanism of PD1/PDL1 blockade. The CD8+ T cell activates upon recognizing the tumor antigen presented on MHC class I and releases IFN-γ to bind to IFN-γ receptor, and consequently induces the expression of PDL1 on tumor cells. PDL1 conjugates the elevated PD1 on T cell surface, triggering inhibitory effect of PD1/PDL1 axis. Anti-PD1 or anti-PDL1 antibody blocks the interaction of PD1 and PDL1, and abolishes the inhibition of CD8+ T cell thus enhancing the antitumor activity.



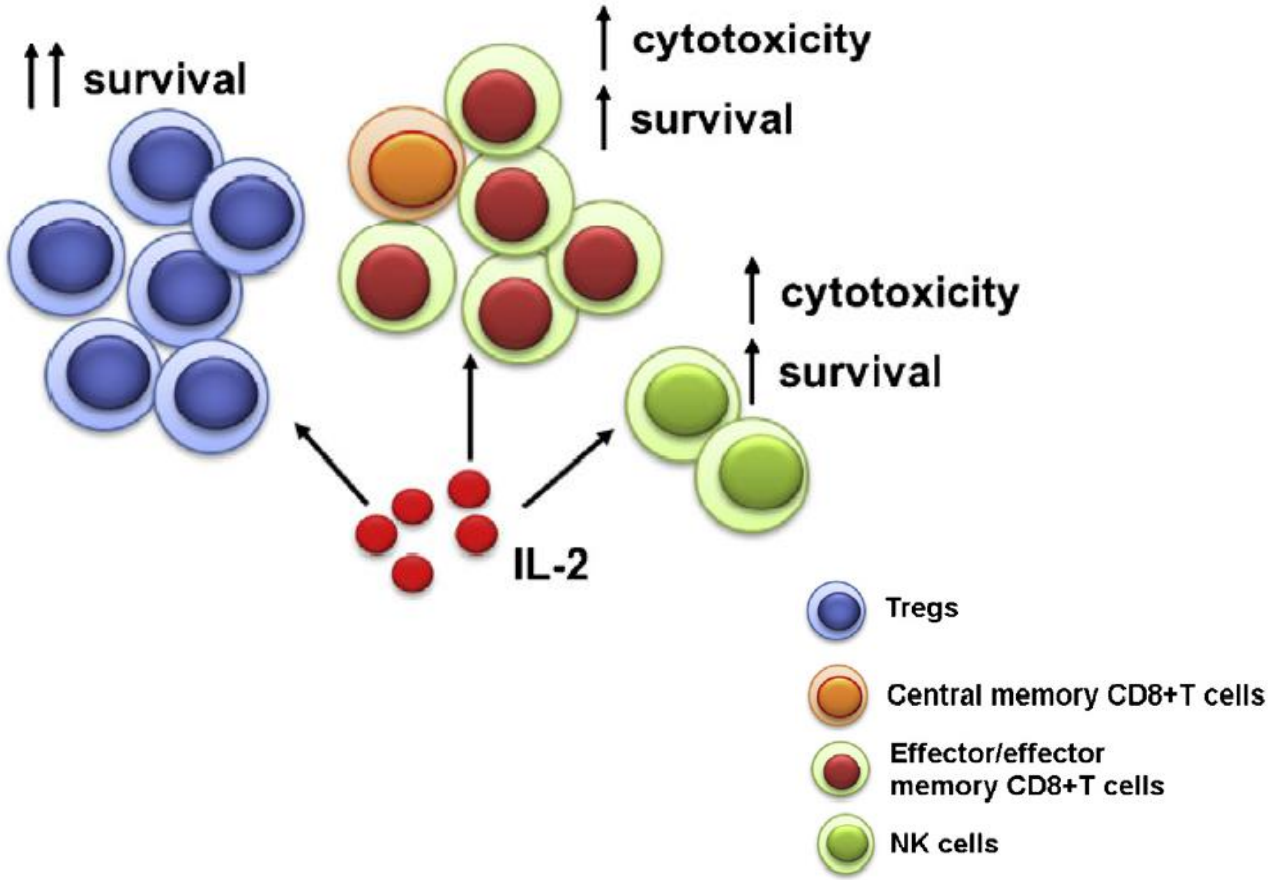
James P. Allison

Tasuku Honjo

The Nobel Prize in Physiology or Medicine 2018 por sua descoberta da terapia do câncer pela inibição da regulação imunológica negativa

Lei, Q., Wang, D., Sun, K., Wang, L., & Zhang, Y. (2020). Resistance mechanisms of anti-PD1/PDL1 therapy in solid tumors. *Frontiers in Cell and Developmental Biology*, *8*.

Terapia com Citocinas



Sim, G. C., & Radvanyi, L. (2014). The IL-2 cytokine family in cancer immunotherapy. *Cytokine & growth factor reviews*, *25*(4), 377-390.

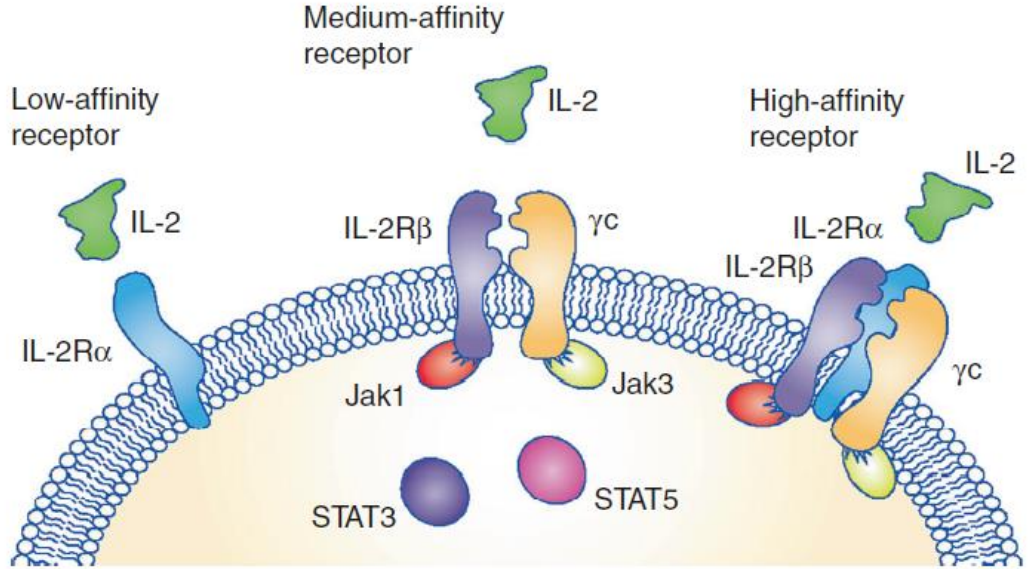


Fig. 1 Interleukin (IL)-2 receptors. IL-2 is recognised by three types of receptor complex expressed on natural killer (NK) and T lymphocytes.

Berraondo, P., Sanmamed, M. F., Ochoa, M. C., Etxeberria, I., Aznar, M. A., Pérez-Gracia, J. L., ... & Melero, I. (2019). Cytokines in clinical cancer immunotherapy. *British journal of cancer*, *120*(1), 6-15.

Terapia com Células T

- ***Terapia adotiva usando células T expressando receptores antigênicos quiméricos (CARs, do inglês*, chimeric antigen receptors*)***
- Os CARs - receptores produzidos por engenharia genética, com sítios de ligação antígeno tumoral específicos codificados por genes variáveis de imunoglobulina (Ig) recombinante e caudas citoplasmáticas contendo domínios de sinalização tanto do TCR como dos receptores de coestimulação.

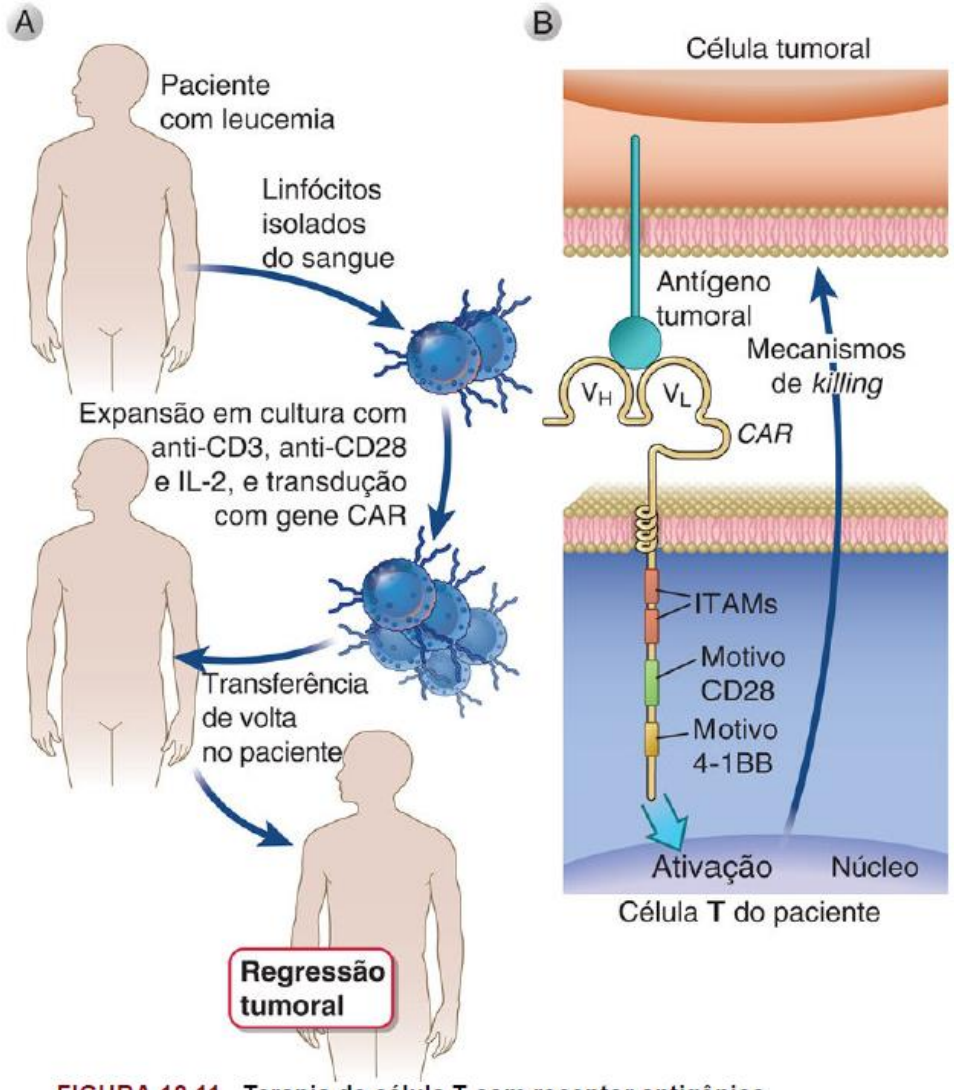
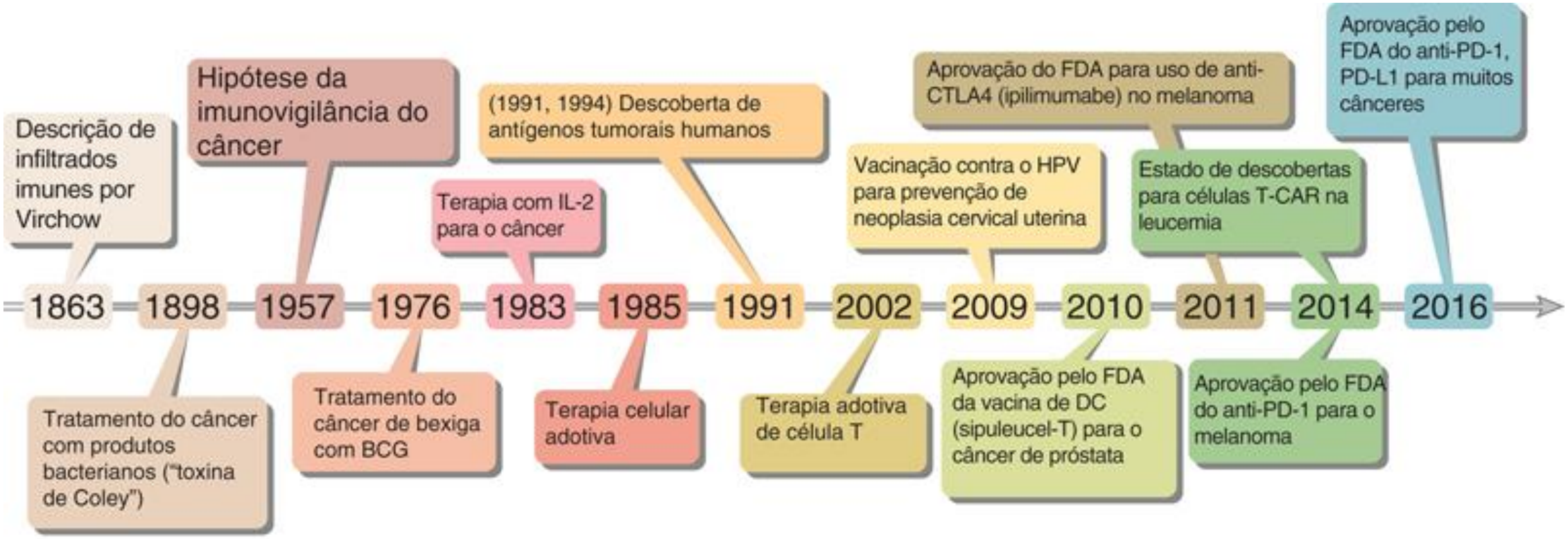


FIGURA 18.11 Terapia de célula T com receptor antigênico quimérico.

História da Imunoterapia do Câncer



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