U.S. Food and Drug Administration
Protecting and Promoting Public Health

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Evolution and Predictions
US FDA Perspective

Ke Liu, MD, PhD

Chief, Oncology Branch

DCEPT, OCTGT, CBER, FDA

November 4, 2015

Global Regulatory Summit

Novel Science on Cancer Immunotherapies

National Harbor, MD

Disclosures

- I have no financial relationships to disclose.
- I will not discuss off-label use.

Breakthrough of the Year 2013

1. Cancer Immunotherapy
2. CRISPR
3. CLARITY
4. Human Stem Cells from Cloning
5. Mini-Organs
6. Cosmic Particle Accelerators
7. Perovskites Solar Cells
8. Why We Sleep
9. Our Microbes, Our Health
10. In Vaccine Design, Looks Do Matter

Outline

- **FDA regulation of oncology products**
- **Reflection on FDA-approved immunotherapies in the last 10 years**
- **Current activities and perspectives**
- **Conclusion**

FDA Regulation of Oncology Products

CDER

Office of Hematology and Oncology Drug Products (OHOP)

- Drugs (small molecules)
- Biologics
  - Monoclonal Antibodies
  - Therapeutic Proteins
  - Cytokines

CBER

Office of Cellular, Tissue and Gene Therapies (OCTGT)

- Cell therapies
- Gene Therapies
- Oncolytic viruses
- Therapeutic vaccines and immunotherapies

CDRH

Office of In Vitro Diagnostics and Radiological Health (OIR)

- Companion Diagnostics

Reflection on Past Approvals

- "Passive" immunotherapy
  - Monoclonal antibodies
- Active immunotherapy
  - Cytokines
  - Microbes (BCGs)
  - Cellular antigen-presenting cell vaccine
  - Oncolytic virotherapy

Past FDA Approvals
--- Immunotherapies (2006-2015) (1)

Year	Product	Indication
2006	Rituximab	First line: diffuse large B-cell, CD20 positive non-Hodgkin's lymphoma (NHL) in combination with CHOP or other anthracycline-based chemo
	Cetuximab	Combo with RT, locally or regionally advanced squamous cell carcinoma of the head and neck (SCCHN) or as a single agent for recurrent or metastatic SCCHN refractory to platinum-based therapy has failed
	Gardasil	Prevention of cervical cancer and other diseases in females caused by Human Papillomavirus
	Bevacizumab	Second-line treatment of metastatic carcinoma of the colon or rectum
	Panitumumab	Metastatic colorectal carcinoma progressed following one or more chemotherapy regimens
	Trastuzumab	Adjuvant treatment of women with node-positive, HER2-overexpressing breast cancer.
2007	Eculizumab	Treatment of paroxysmal nocturnal hemoglobinuria
2008	Bevacizumab	Combo with chemo for 1st line treatment of metastatic HER2 negative breast cancer. Revoked in 2011
	Denileukin diftitox	Conversion from accelerated approve to traditional approval: treatment of persistent or recurrent CD-25 positive cutaneous T-cell lymphoma
2009	Bevacizumab	• Single agent treatment for glioblastoma progressed after prior therapy • Combination with interferon alfa for the treatment of patients with metastatic renal cell carcinoma
	Ofatumumab	Treatment of chronic lymphocytic leukemia (CLL) refractory to fludarabine and alemtuzumab

Past FDA Approvals
--- Immunotherapies (2006-2015) (2)

Year	Product	Indication
2010	Rituximab	In combination with fludarabine and cyclophosphamide (FC), for the treatment of previously untreated and previously treated CLL
	Sipuleucel-T	Treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer.
	Gemtuzumab	Pfizer Inc., in agreement with the FDA, voluntarily discontinued the commercial marketing
	Trastuzumab	In combination with cisplatin and a fluoropyrimidine (capecitabine or 5-fluorouracil), for 1st line treatment of HER2 overexpressing metastatic gastric or gastroesophageal (GE) junction adenocarcinoma
	Denosumab	Prevention of skeletal-related events (SREs) in patients with bone metastases from solid tumor
2011	Rituximab	For maintenance therapy for previously untreated follicular, CD-20 positive, B-cell non-Hodgkin lymphoma responded to rituximab in combination with chemotherapy
	Ipilimumab	for the treatment of unresectable or metastatic melanoma.
	Brentuximab vedotin	• Treatment of Hodgkin lymphoma after failure of autologous stem cell transplant (ASCT) or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not ASCT candidates • Treatment of systemic anaplastic large cell lymphoma (ALCL) after failure of at least one prior multi-agent chemotherapy regimen.
	Cetuximab	In combination with platinum-based therapy plus 5-florouracil (5-FU) for the first-line treatment of patients with recurrent locoregional disease and/or metastatic SCCHN.

Past FDA Approvals
--- Immunotherapies (2006-2015) (3)

Year	Product	Indication
2012	Pertuzumab	In combination with trastuzumab and docetaxel for 1st line treatment of patients with HER2-positive metastatic breast cancer
	Cetuximab	In combination with FOLFIRI (irinotecan, 5-fluorouracil, leucovorin) for first-line treatment of patients with K-ras mutation-negative (wild-type), EGFR-expressing metastatic colorectal cancer (mCRC) as determined by FDA-approved tests for this use
	ziv-aflibercept	In combination with FOLFIRI for the treatment of patients with metastatic colorectal cancer (mCRC) resistant to or progressed following an oxaliplatin containing regimen
2013	Bevacizumab	In combination with fluoropyrimidine-irinotecan or fluoropyrimidine-oxaliplatin based chemotherapy for the treatment of patients with metastatic colorectal cancer (mCRC) whose disease has progressed on a first-line bevacizumab-containing regimen
	Ado-trastuzumab emtansine	Single agent for the treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either received prior therapy for metastatic disease or developed disease recurrence during or within six months of completing adjuvant therapy
	Denosumab	Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity
	Pertuzumab	In combination with trastuzumab and docetaxel for the neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer
	obinutuzumab	in combination with chlorambucil for 1st line treatment of CLL

Past FDA Approvals
--- Immunotherapies (2006-2015) (4)

Year	Product	Indication
2014	Ofatumumab	In combination with chlorambucil, for the treatment of previously untreated patients with chronic lymphocytic leukemia (CLL), for whom fludarabine-based therapy is considered inappropriate
	Ramucirumab	• Single agent for the treatment of patients with advanced or metastatic, gastric or gastroesophageal junction (GEJ) adenocarcinoma with disease progression on or after prior treatment with fluoropyrimidine- or platinum-containing chemotherapy • In combination with paclitaxel for treatment of advanced gastric or GEJ adenocarcinoma. • in combination with docetaxel for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with disease progression on or after platinum-based chemotherapy
	Siltuximab	Treatment of patients with multicentric Castleman's disease (MCD) who are human immunodeficiency virus (HIV-) -negative and human herpes virus -8 (HHV-8) -negative
	Bevacizumab	• Treatment of persistent, recurrent or metastatic cervical cancer, in combination with paclitaxel and cisplatin or paclitaxel and topotecan • In combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan for the treatment of patients with platinum-resistant, recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer
	Pembrolizumab	Treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor
	Blinatumomab	Treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (R/R ALL)
	Nivolumab	Treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor

Past FDA Approvals
--- Immunotherapies (2006-2015) (5)

Year	Product	Indication
2015	Nivolumab	• Metastatic squamous non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy • metastatic non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving nivolumab
	Dinutuximab	In combination with granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-2 (IL-2), and 13-cis-retinoic acid (RA), for the treatment of pediatric patients with high-risk neuroblastoma who achieve at least a partial response to prior first-line multiagent, multimodality therapy
	Ramucirumab	In combination with FOLFIRI for the treatment of patients with metastatic colorectal cancer (mCRC) whose disease has progressed on a first line bevacizumab-, oxaliplatin- and fluoropyrimidine-containing regimen
	Brentuximab vedotin	For the post-autologous hematopoietic stem cell transplantation (auto-HSCT) consolidation treatment of patients with classical Hodgkin lymphoma (HL) at high risk of relapse or progression
	Nivolumab + ipilimumab	For the treatment of patients with BRAF V600 wild-type, unresectable or metastatic melanoma
	Pembrolizumab	Treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express programmed death ligand 1 (PD-L1) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy.
	Idarucizumab	Treatment of patients treated with dabigatran (Pradaxa) when reversal of the anticoagulant effects of dabigatran is needed for emergency surgery/urgent procedures, or in life-threatening or uncontrolled bleeding

Past FDA Approvals
--- Immunotherapies (the week of October 25, 2016)

Product	Indication
Talimogene Laherparepvec	IMLYGIC is a genetically modified oncolytic viral therapy indicated for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery. (Limitations of use: IMLYGIC has not been shown to improve overall survival or have an effect on visceral metastases.)
Ipilimumab	Adjuvant treatment of patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy

An Analysis of FDA-approved Immunotherapy Indications (2006-2015)

- A total of 161 approved indications
- 48 of them (~30%) immunotherapy-related
- 44 for monoclonal antibodies ← "Passive" Immunotherpay
- 2 for HPV vaccines
- 1 for cellular cancer vaccine

Active Immunotherpay

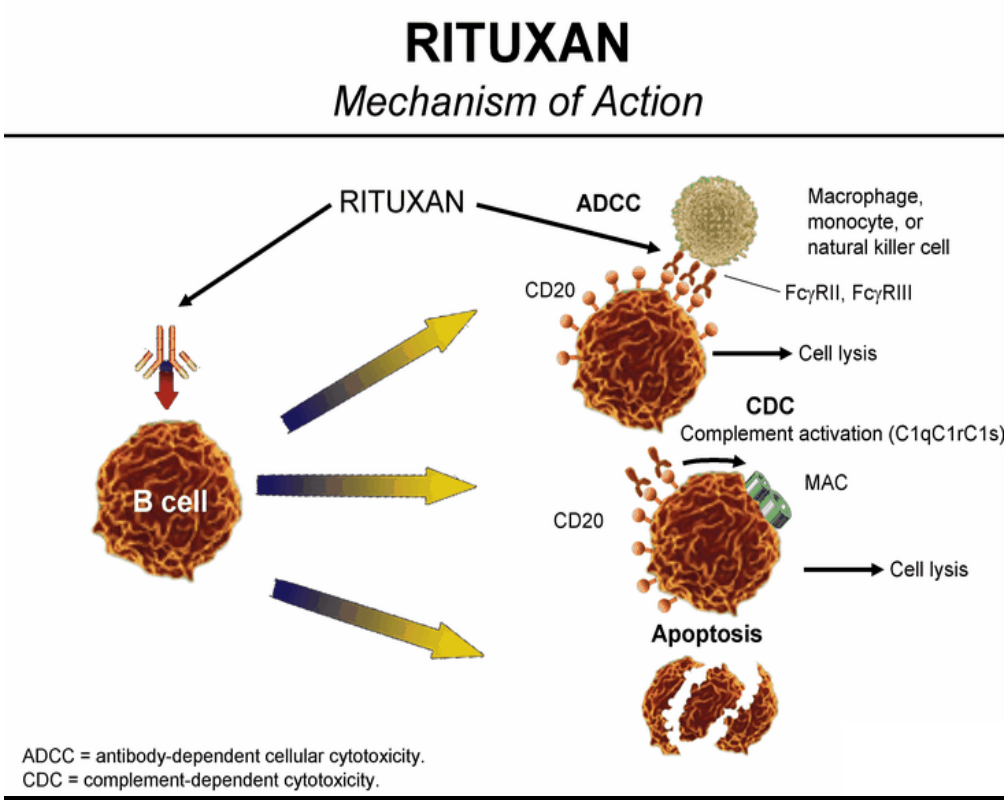
- 1 for oncolytic virus (genetically modified)

Monoclonal Antibodies

Theme 1: Naked antibody against its cognate antigen on tumor cells

Examples:

- Rituximab
- Ofatumumab
- Obinutuzumab



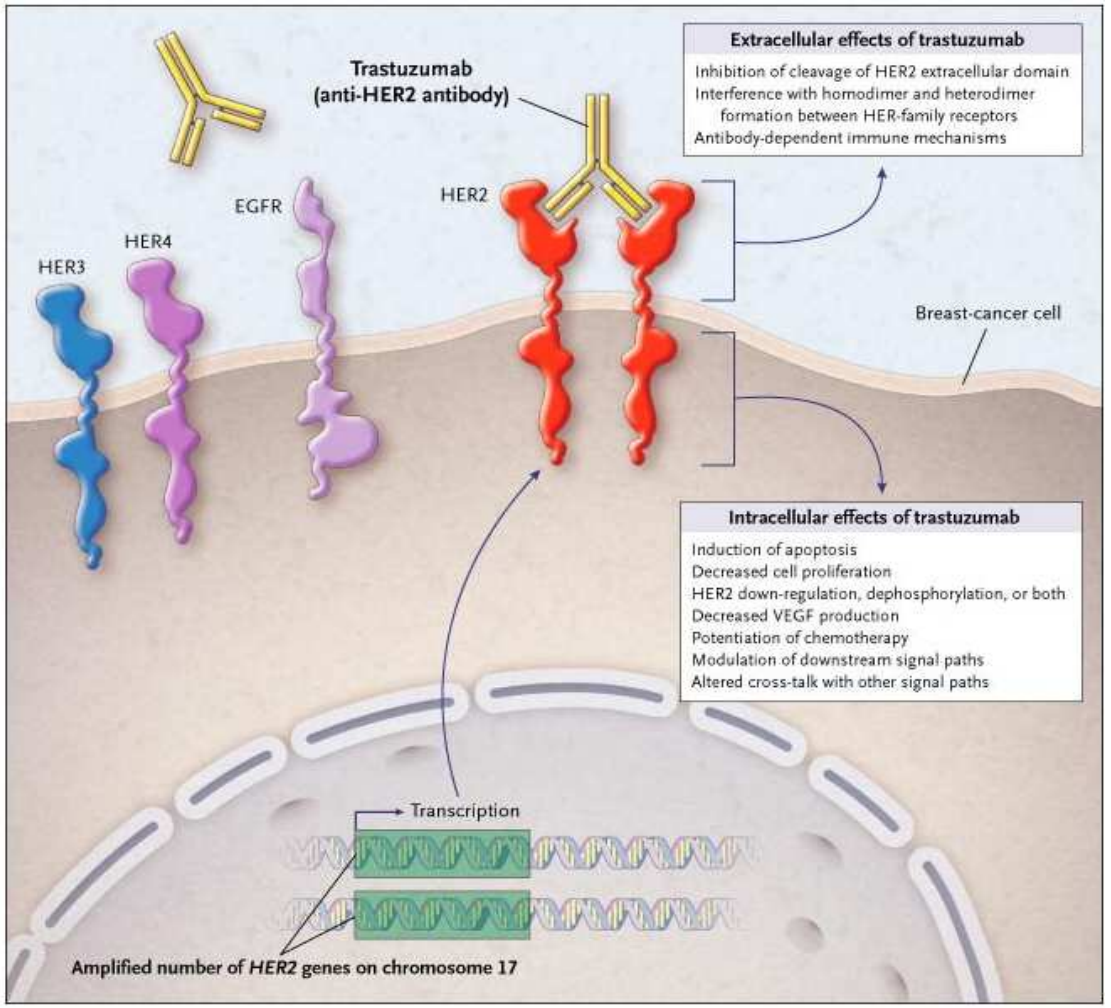
Monoclonal Antibodies

Theme 2:

Naked antibody against its target that controls or is involved in the cell growth (e.g., receptor)

Examples:

- Trastuzumab
- Cetuximab
- Panitumumab
- Ramucirumab



Burstein HJ. N Engl J Med 2005;353:1652-1654.

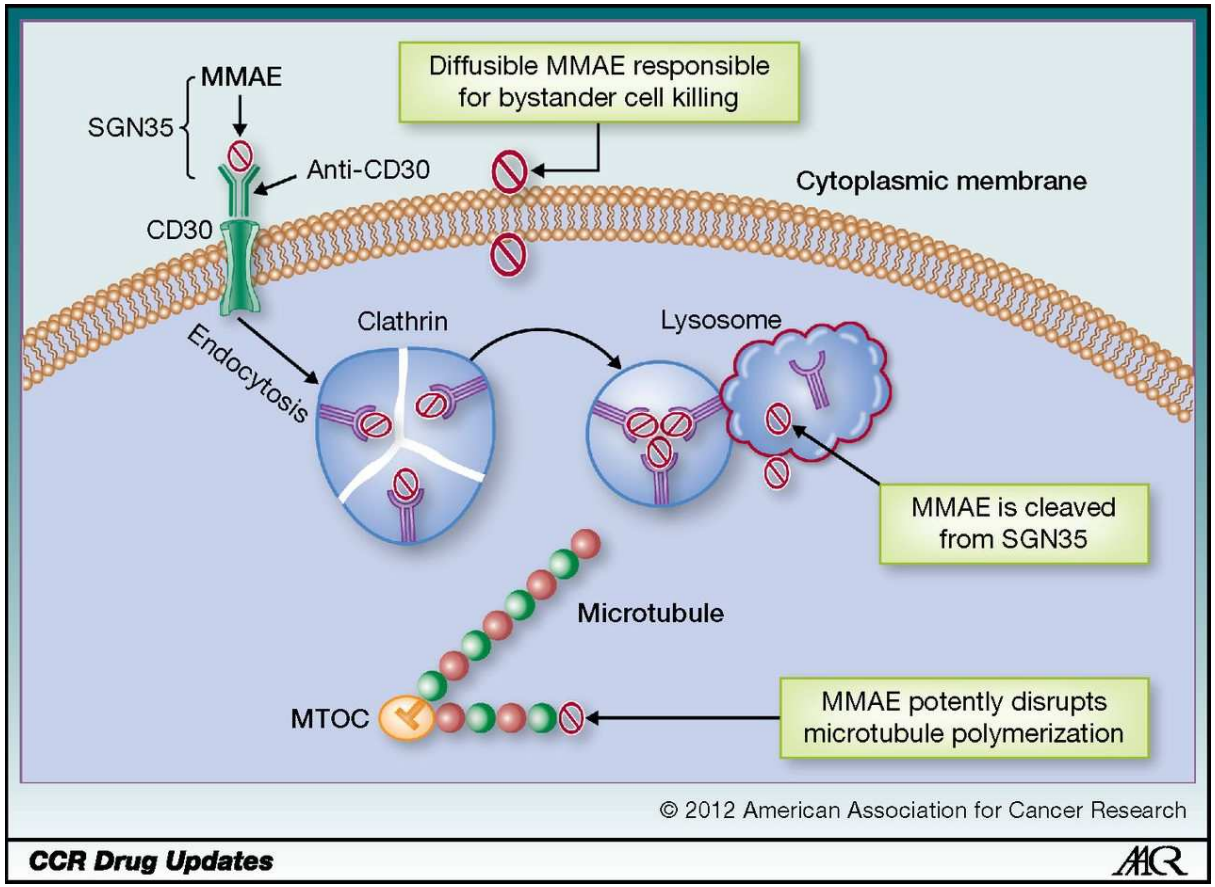
Monoclonal Antibodies

Theme 3:

Conjugated with toxin

Examples:

- Brentuximab vedotin
- Ado-trastuzumab emtansine



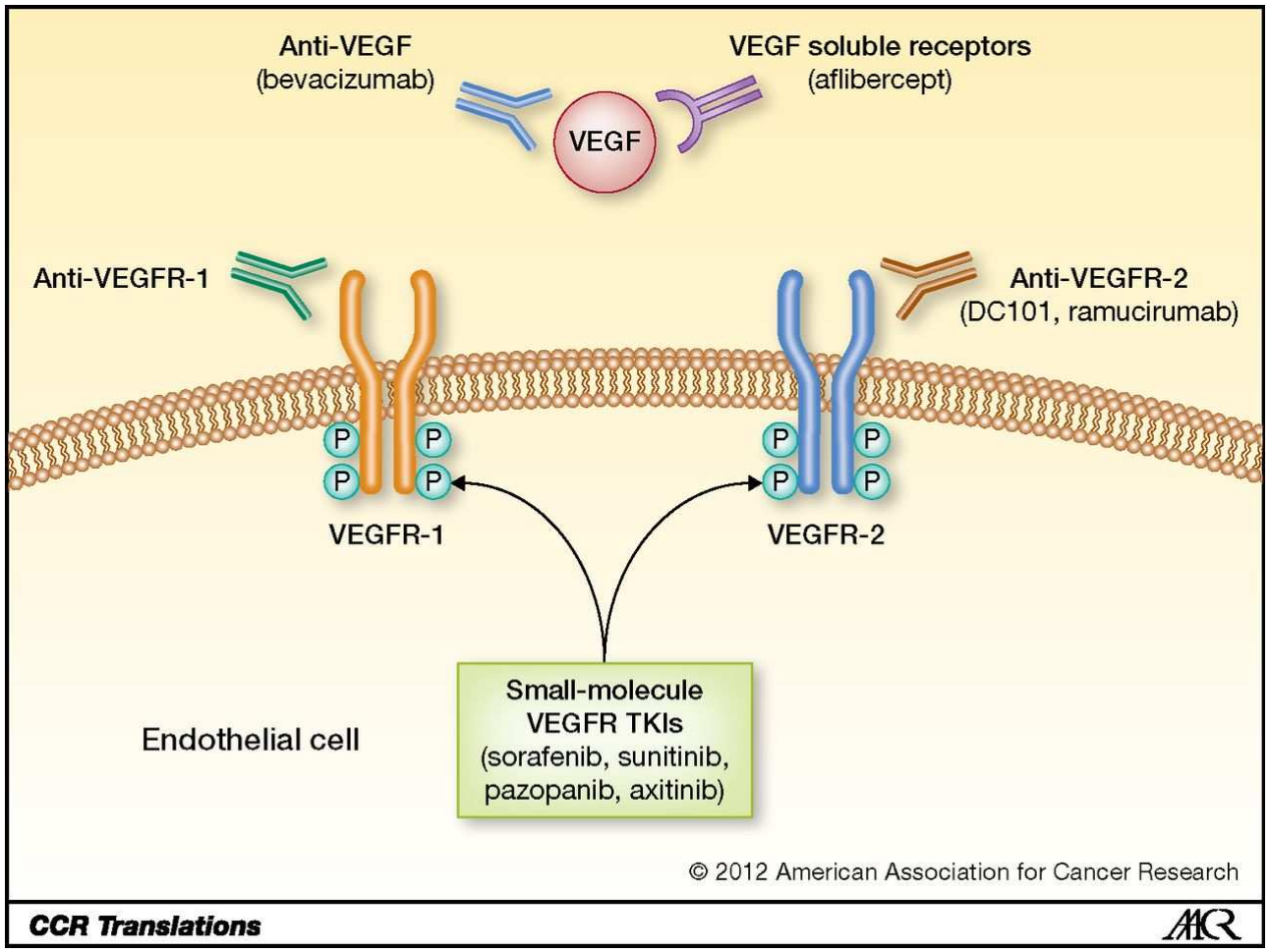
Monoclonal Antibodies

Theme 4:

Anti-growth Factors (extracellular)

Examples:

- Bevacizumab
- Denosumab
- Aflibercept



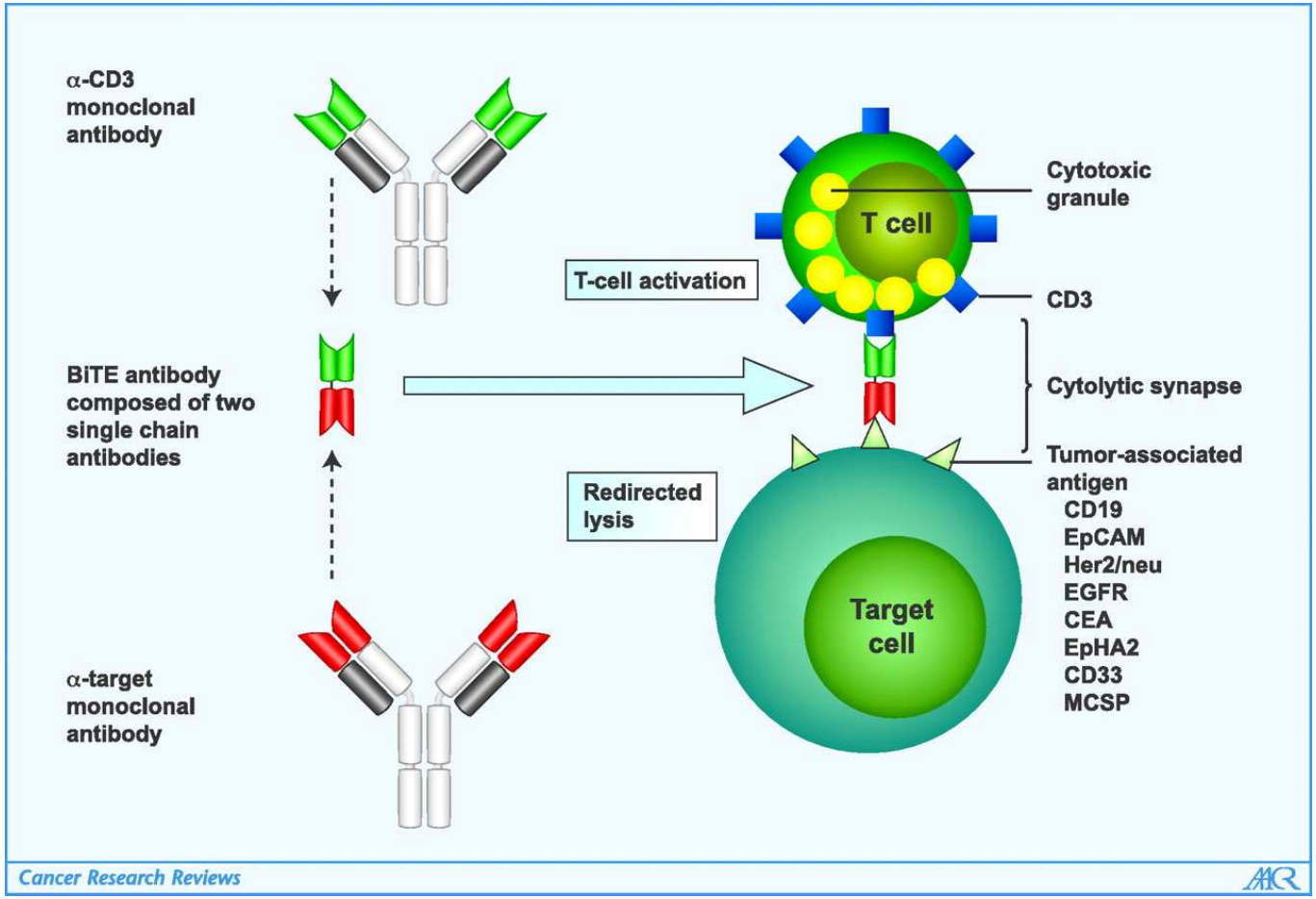
Monoclonal Antibodies

Theme 5:

Bi-specific T-cell engager (BiTE)

Example:

Blinatumomab



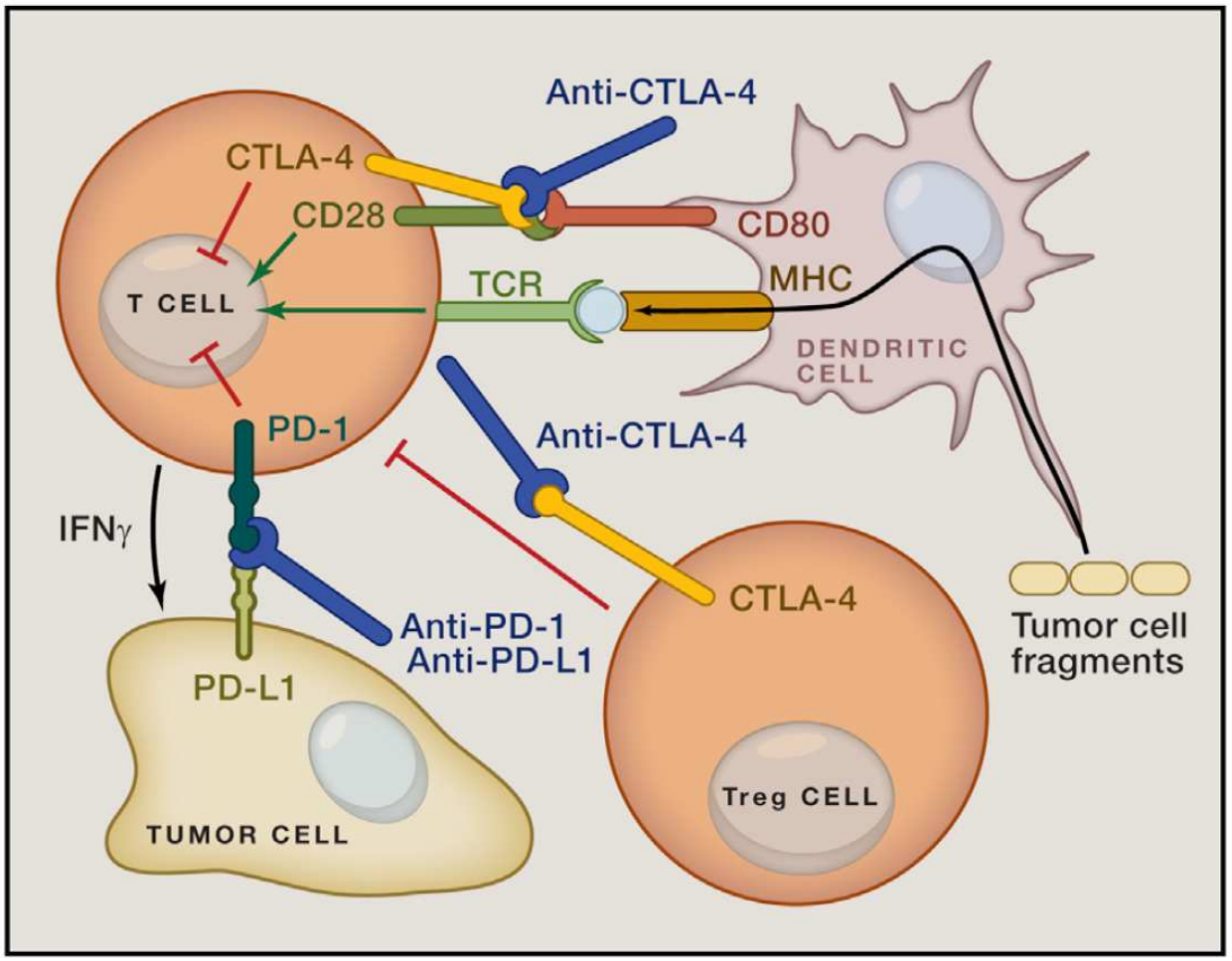
Monoclonal Antibodies

Theme 6:

Checkpoint Inhibitors

Examples:

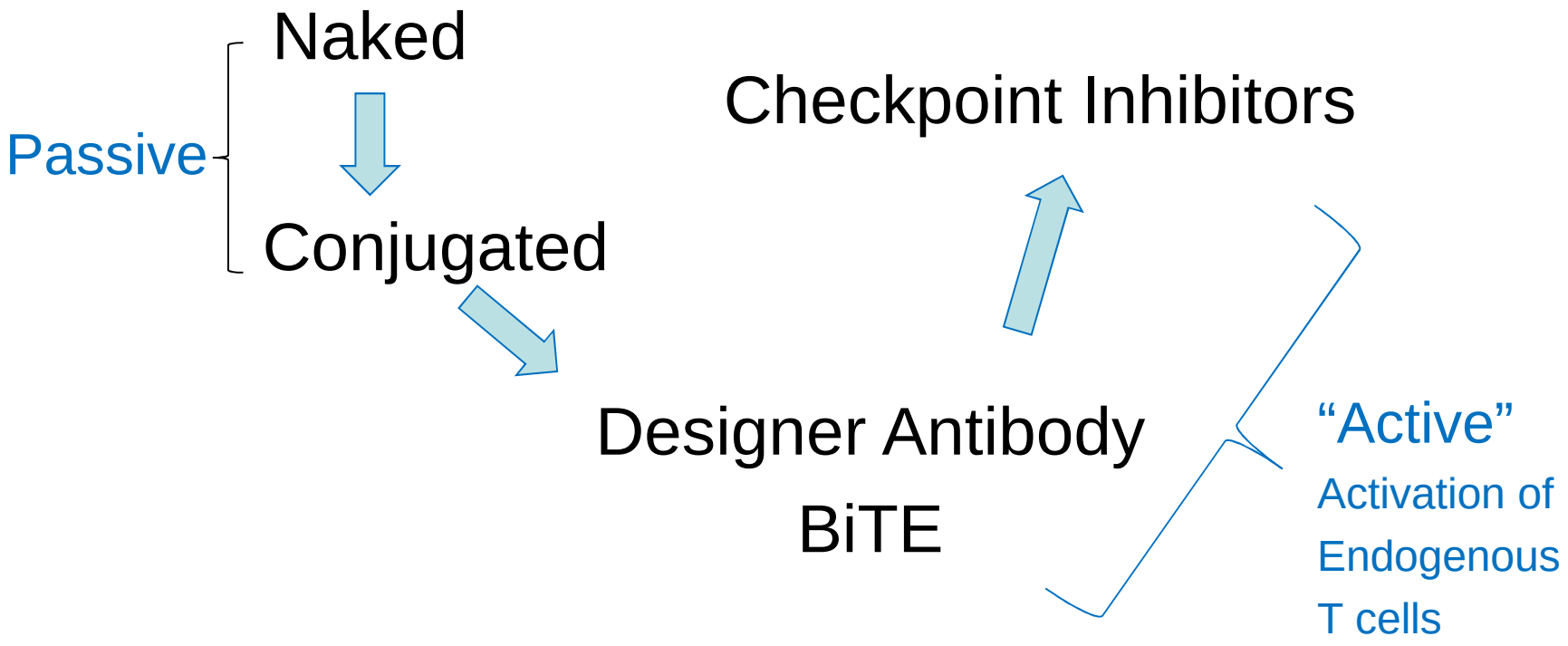
- α–CTLA-4:
  Ipilimumab
- α–PD1
  Nivolumab
  Pembrolizumab



Miller and Sadelain Cancer Cell 27, April 13, 201

Summary (Monoclonal Antibodies)

- Mainstay treatment in hem/onc practice
- Tremendous evolution in the last several decades:

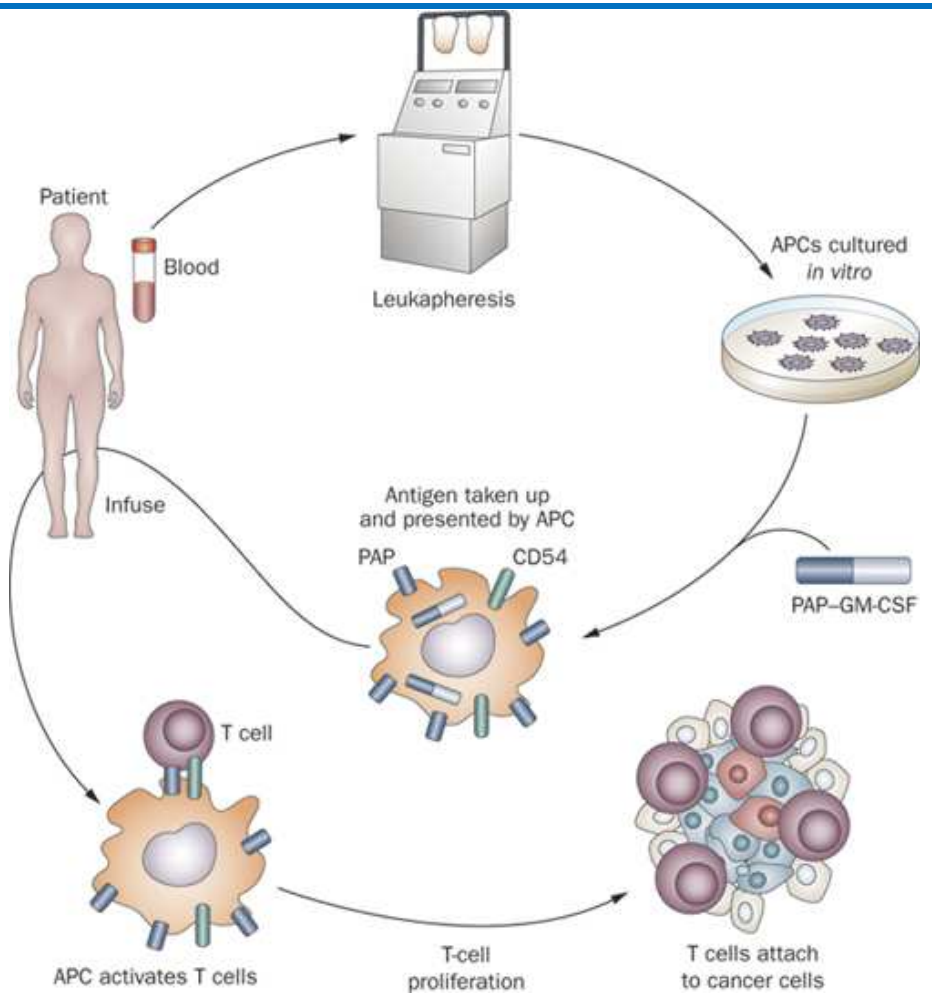


Active Immunotherapy

- sipuleucel-T for prostate cancer
- Talimogene laherparepvec for melanoma lesions
- Two BCG products for superficial bladder cancer (approved in 1990's)
- Interleukin-2 (approved in 90's), Interferon α (80's)

sipuleucel-T

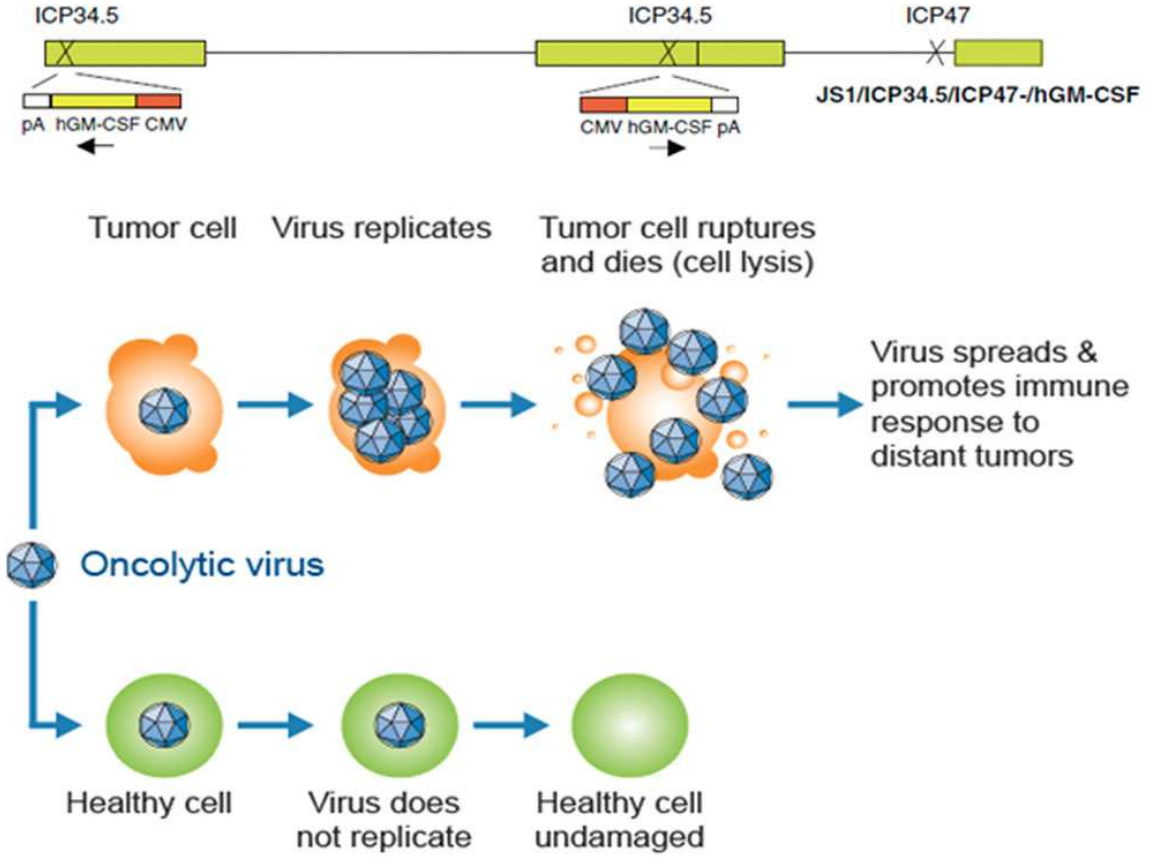
Antigen-presenting Cells (APC) pulsed with PAP-GM-CSF



Nat. Rev. Clin. Oncol. c.2011.72

Talimogene laherparepvec

Genetically modified oncolytic herpes simplex virus-1



J. Surg. Oncol. 2014;109:320–326.

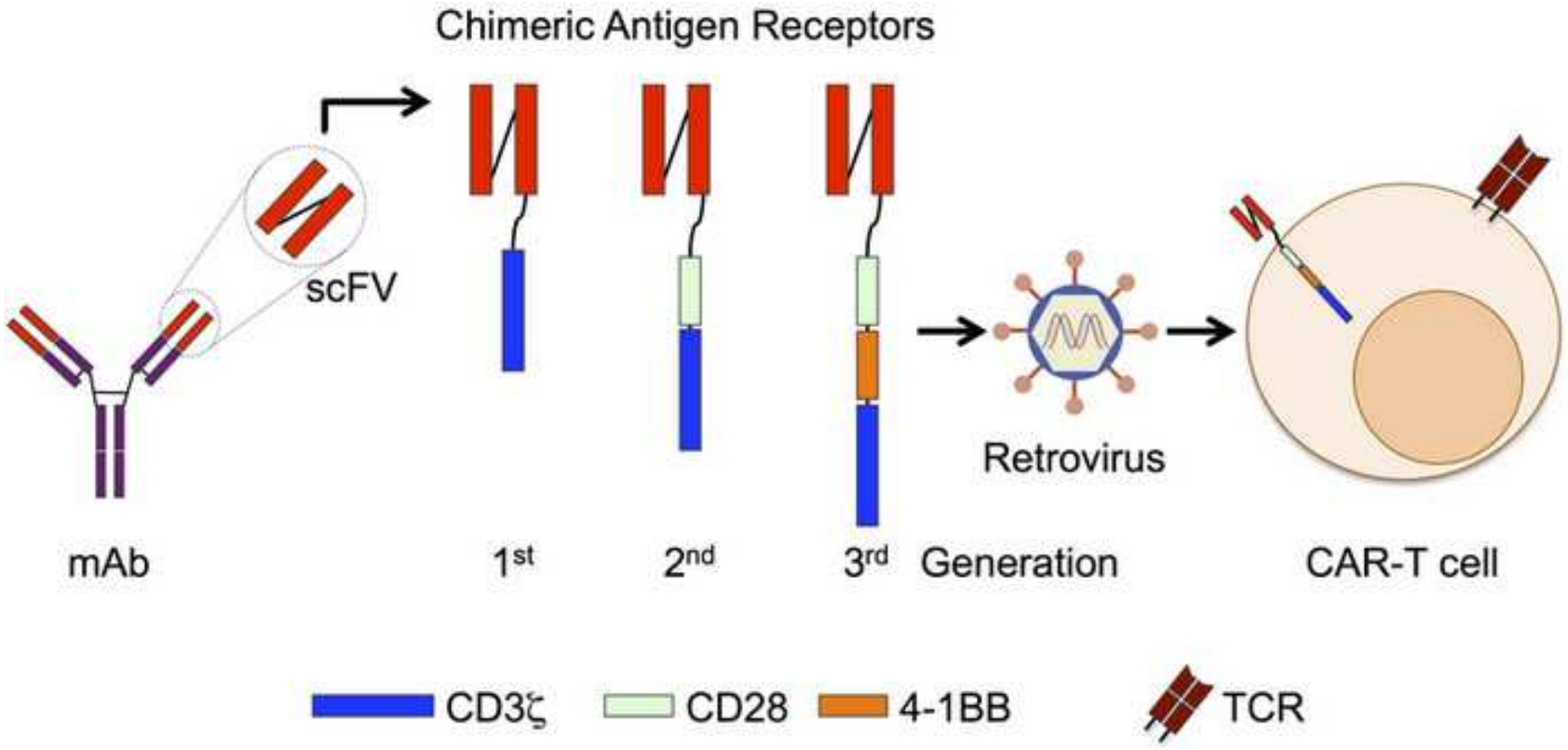
Evolution (Active Immunotherapy)

- Considerable
- From non-specific treatment to complicated cell and gene therapy

Perspectives

- Further expansion of investigations on
  - Releasing the brake [e.g., checkpoint inhibitors (MoAb and small molecules), anti-PD1, anti-PDL1]
  - Novel mechanism of action (e.g.,BiTE)
  - Oncolytic virotherapy
- CAR – T cells and adoptive immunotherapy
- Personalized vaccine based on unique antigens rather than shared tumor antigens
- Combination
- Biomarker

Chimeric Antigen Receptor-Modified T cells (CAR-T)

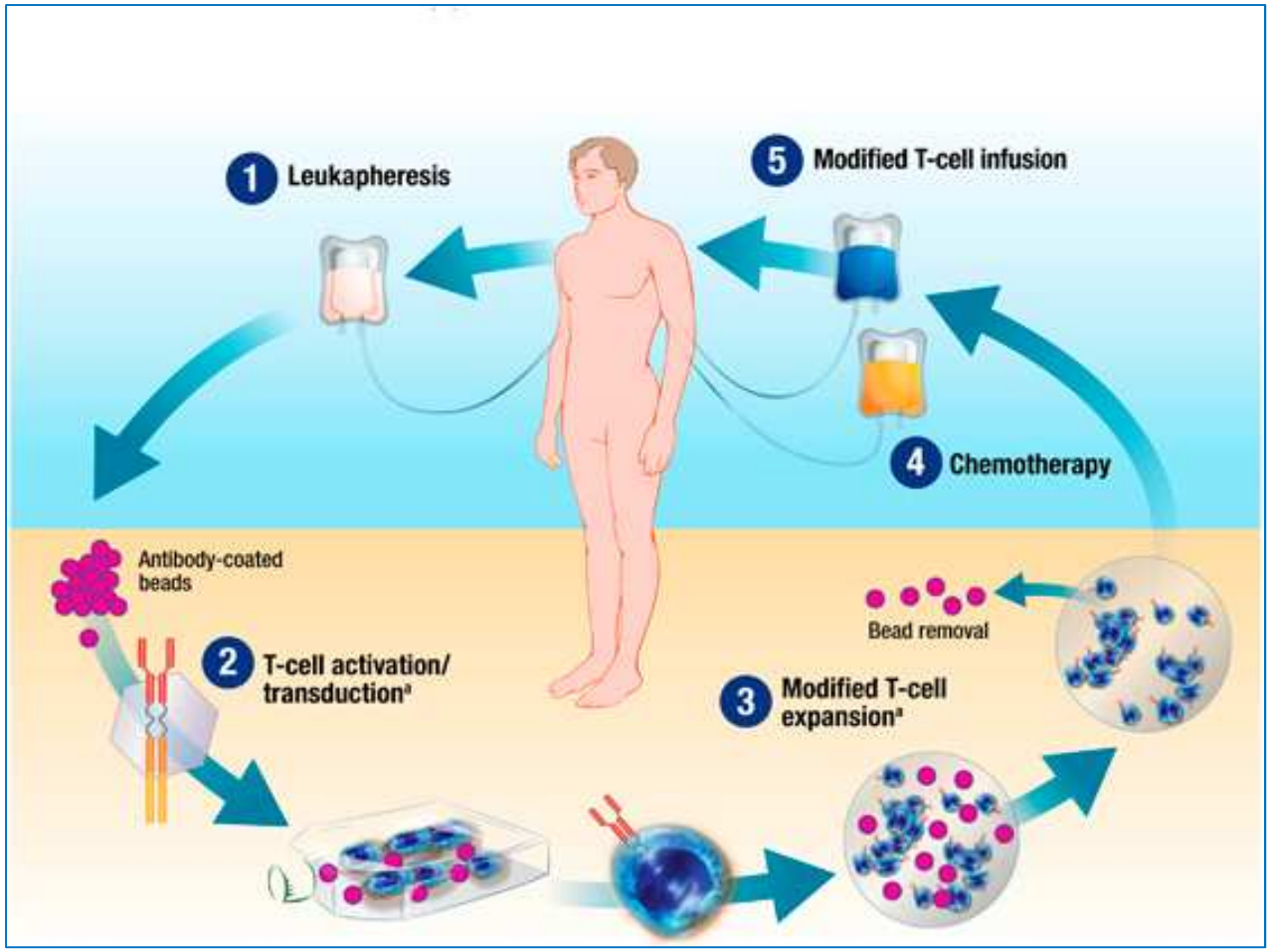


Michael S. Magee, Adam Snook. Discovery Medicine, Vol 100, November 17, 2014

CAR-T Cell Therapy

Performance-enhancing drugs: design and production of redirected (CAR) T cells

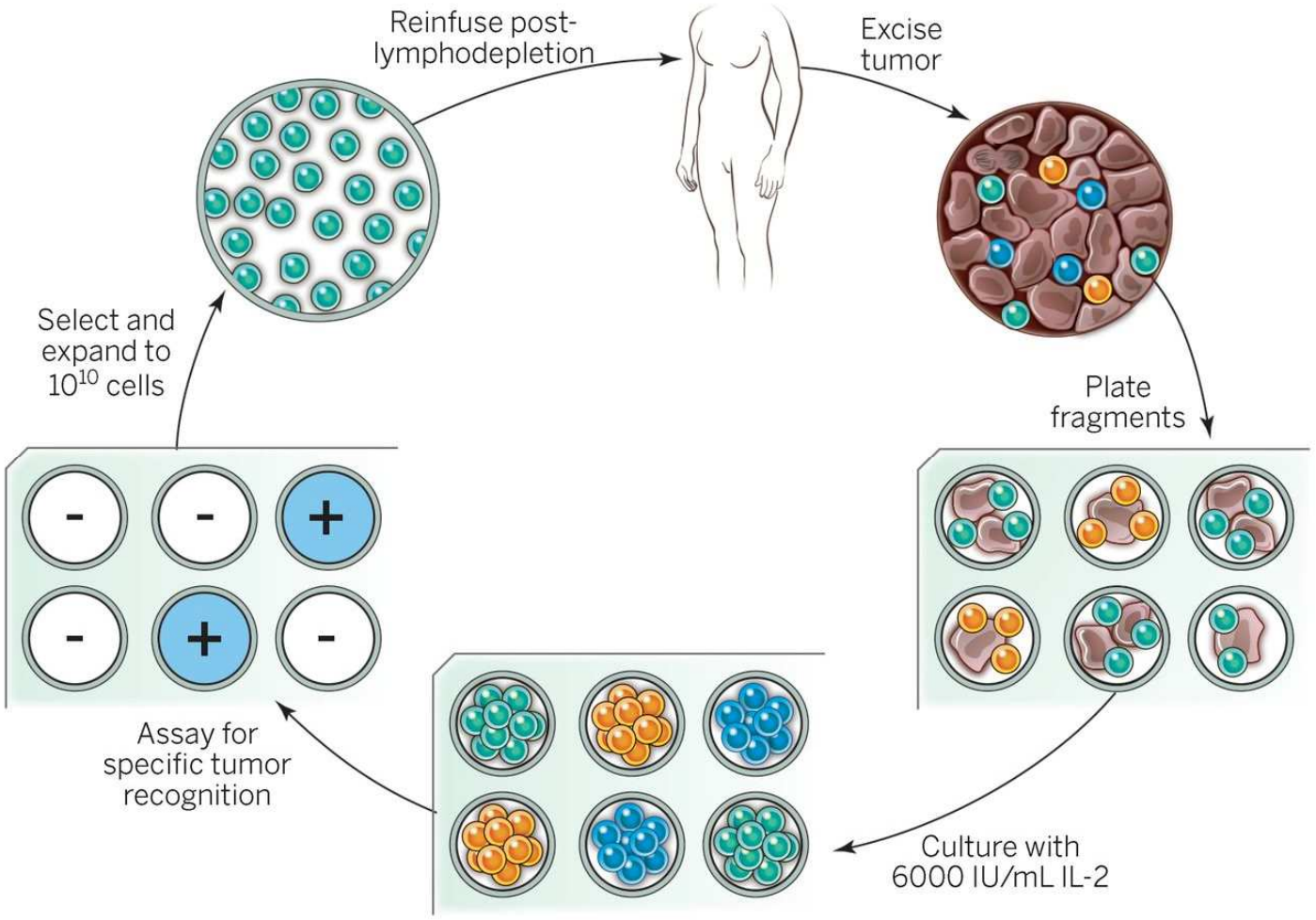
B L Levine
Cancer Gene Therapy (2015) 22, 79–84



INDs for Genetically Modified T-cells in US

- 106 INDs as of October 8, 2015
- 36 (~ 30%) of them (CAR-T INDs) targeting CD19
- Promising anti-tumor activities, especially in leukemias (70-90% CRs reported in relapsed and/or recurrent ALL)
- Challenges
  - Manufacturing and controls
  - Toxicity management (e.g., cytokine-release syndrome)
  - Trial design (e.g., patient population, efficacy endpoint and evaluation)

Adoptive Cell Therapy (ACT)



Overall tumor responses in melanoma: 30% to 60% reported.

Steven A. Rosenberg, and Nicholas P. Restifo Science 2015;348:62-68

T cells Recognizing Tumor-specific Mutations

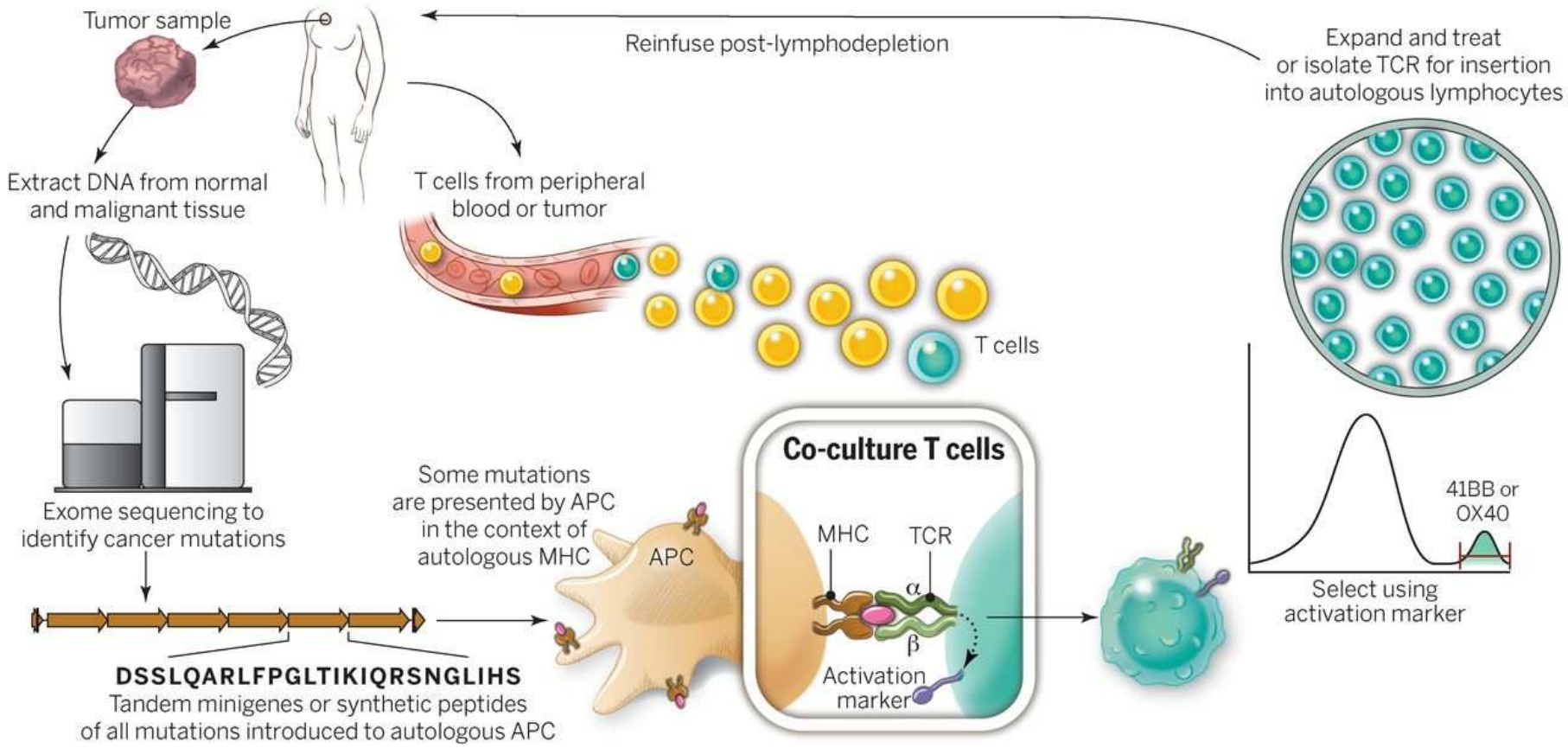
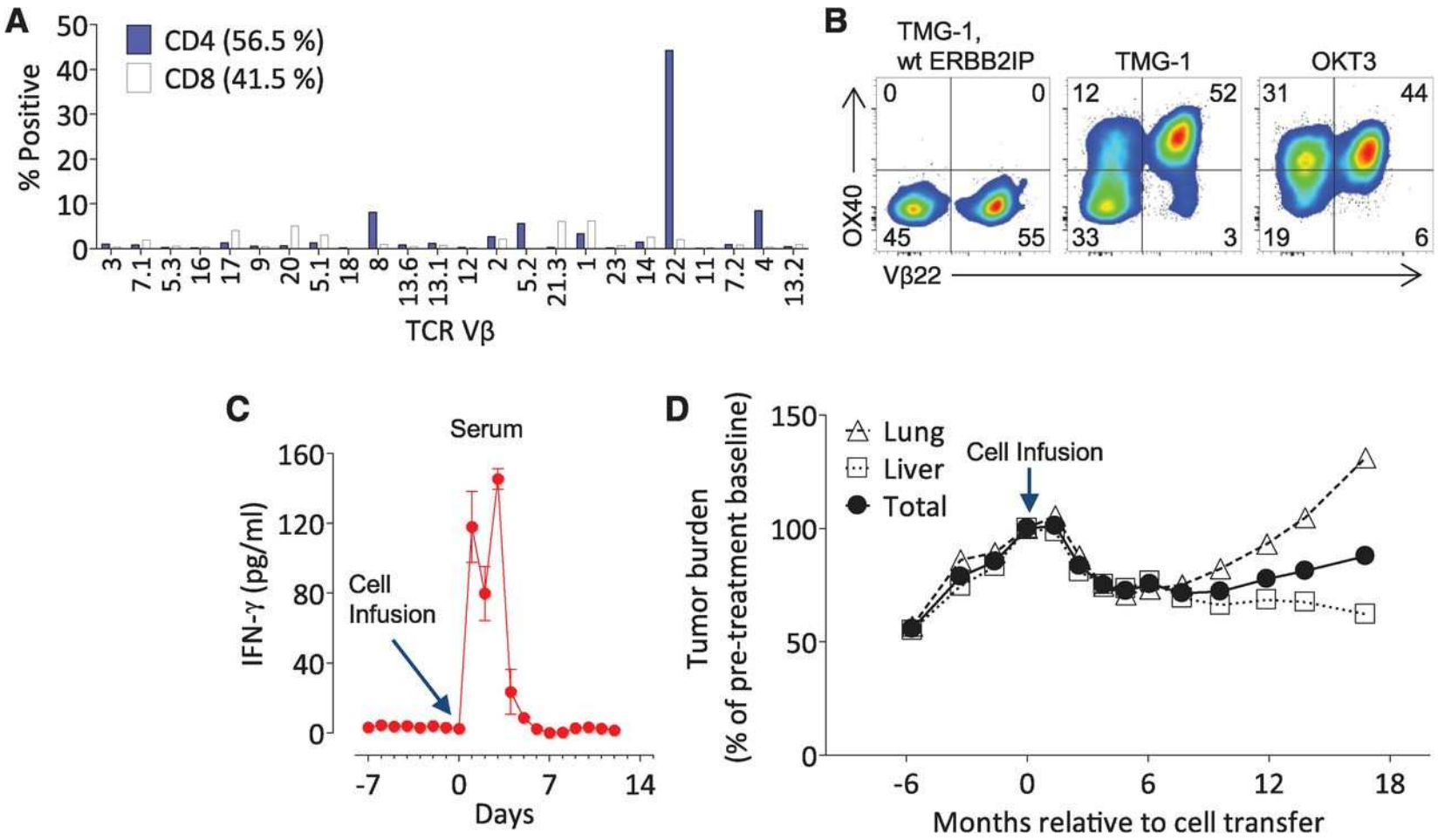
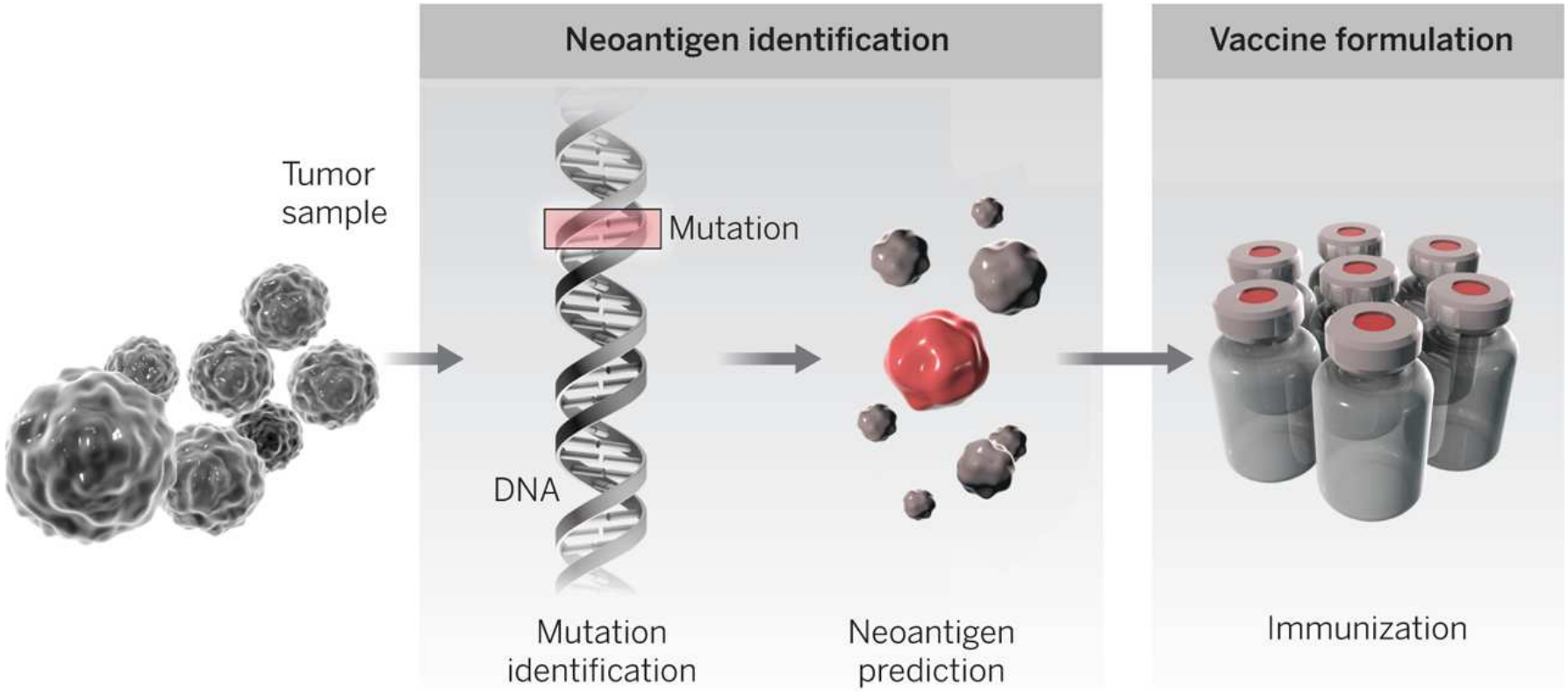


Fig. 2 Adoptive transfer of TIL containing ERBB2IP mutation–reactive T cells.(A) Flow-cytometric analysis of the TCR-Vβ repertoire of 3737-TIL, gated on live CD4+ or CD8+ T cells.



Eric Tran et al. Science 2014;344:641-645

Personalized Cancer Vaccine (Neoantigen Approach) (1)



Lélia Delamarre et al. Science 2015;348:760-761

Personalized Cancer Vaccine (Neoantigen Approach) (2)

Potential advantages

- Pre-existing immunity to neoantigen, further augmented by vaccination
- Less chance of developing tolerance
- Less chance of autoimmune reaction

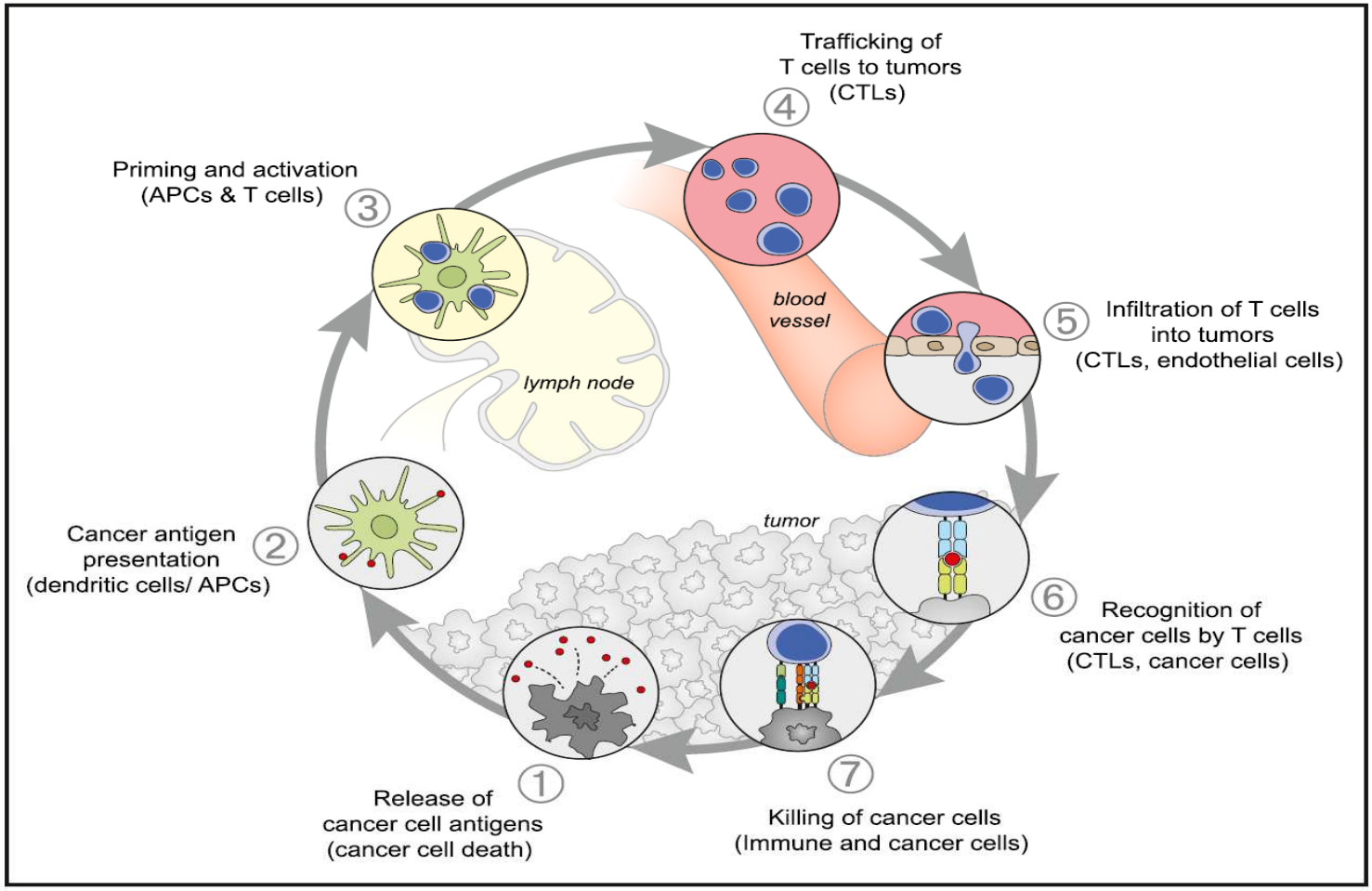
Personalized Cancer Vaccine (Neoantigen Approach) (3)

Challenges

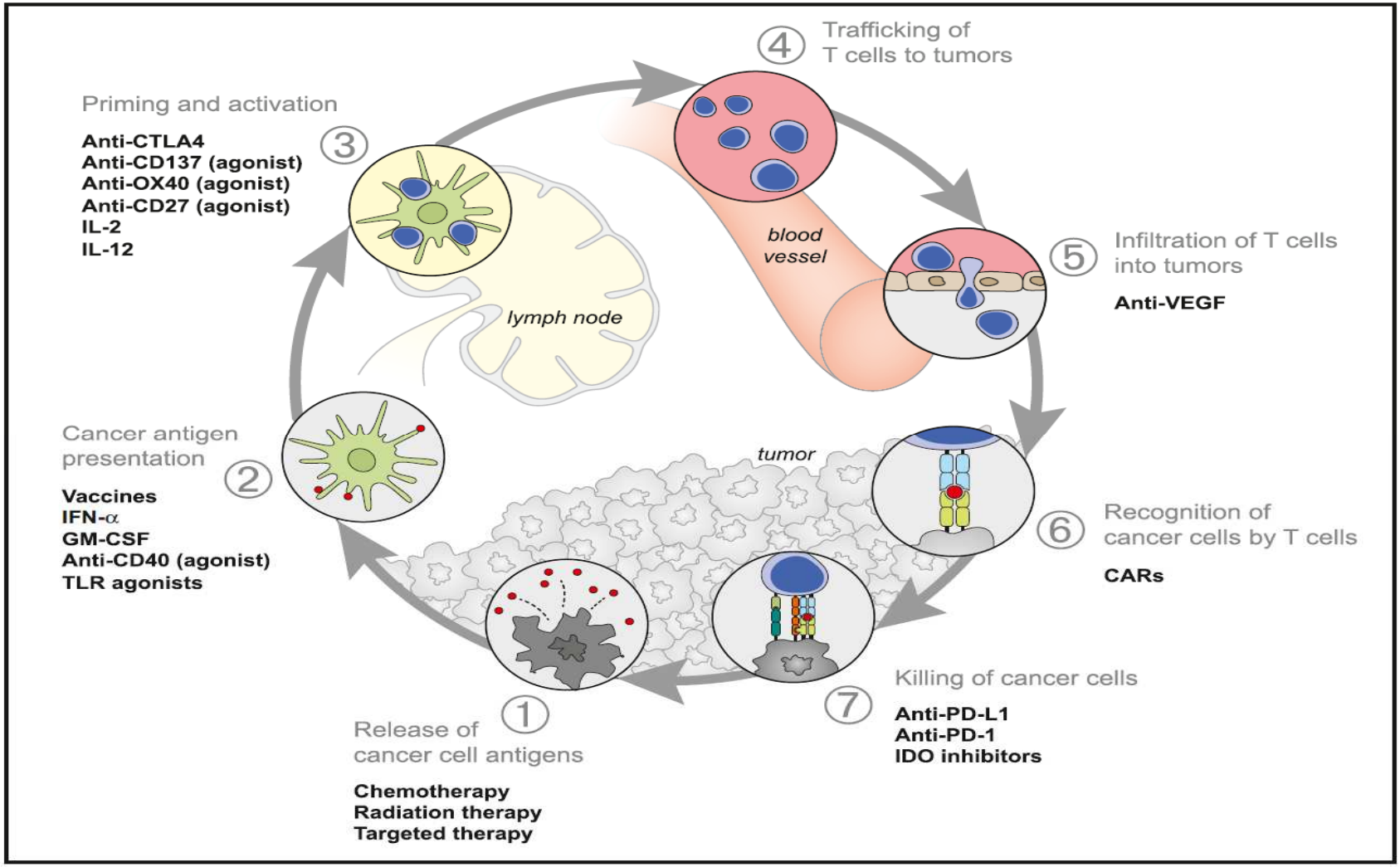
- Algorithm in selecting appropriate neoantigen (maybe too many from a given tumor)
- Exome sequence technology, next-generation sequencing (NGS) and standardization
- Regulatory challenge:
  - A patient may receive a mixture of different products instead of conventionally one product at a time
  - Product from each patient is different from other patients

Combination of Immunotherapeutics

Cancer Immunity Cycle



Therapies that Might Affect Cancer Immunity Cycle



Combination of Immunotherapeutics

- Fertile ground for combination
- Synergistic or complementary mechanism of actions from different agents
- Expect to see expansion of more combination trials
- Approval of first combination of immunotherapeutics --- Ipilimunab + Nivolumab in untreated melanoma

Combination of Nivolumab and Ipilimumab

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

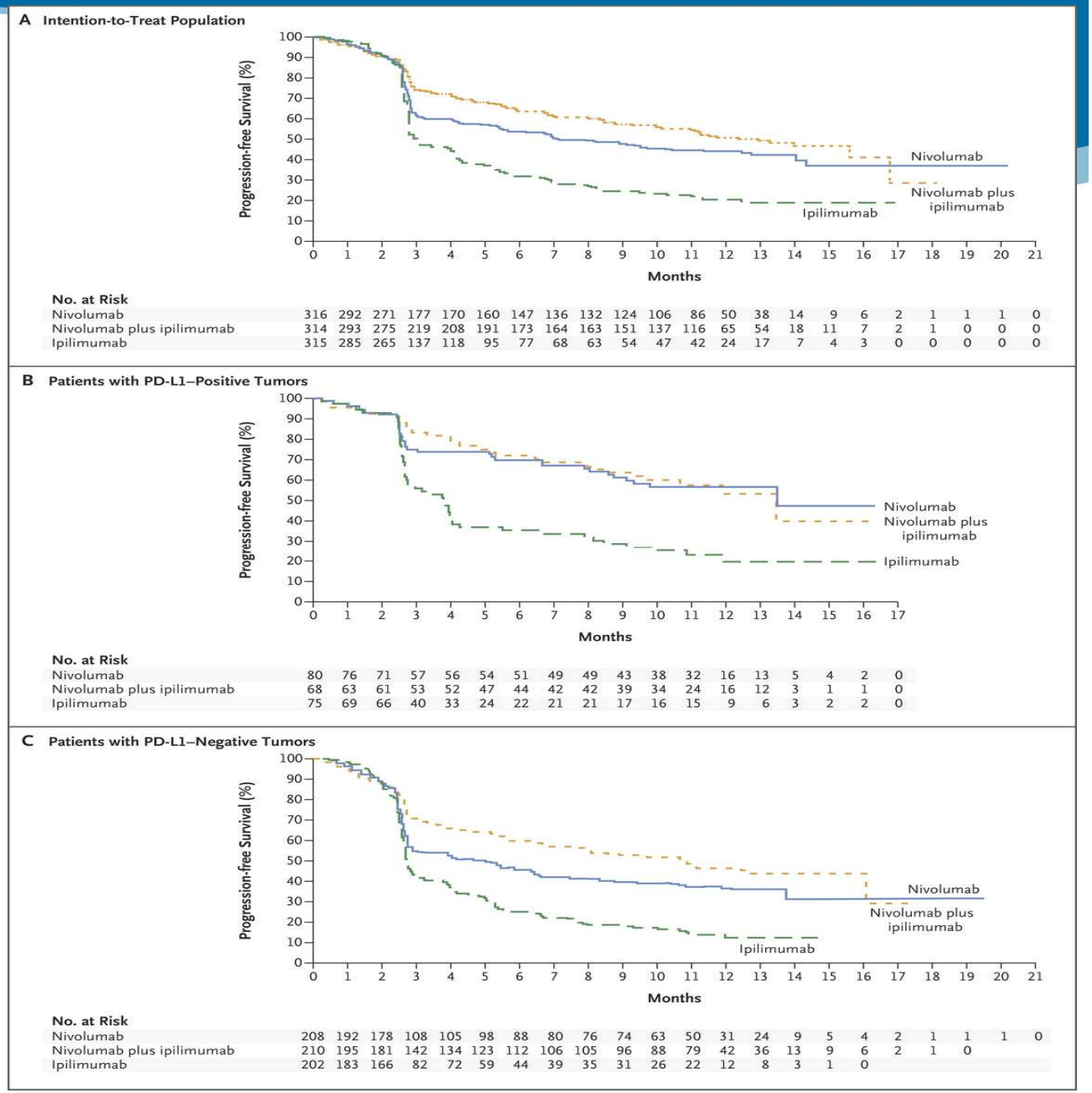
Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma

J. Larkin, V. Chiarion-Sileni, R. Gonzalez, J.J. Grob, C.L. Cowey, C.D. Lao, D. Schadendorf, R. Dummer, M. Smylie, P. Rutkowski, P.F. Ferrucci, A. Hill, J. Wagstaff, M.S. Carlino, J.B. Haanen, M. Maio, I. Marquez-Rodas, G.A. McArthur, P.A. Ascierto, G.V. Long, M.K. Callahan, M.A. Postow, K. Grossmann, M. Sznol, B. Dreno, L. Bastholt, A. Yang, L.M. Rollin, C. Horak, F.S. Hodi, and J.D. Wolchok

Larkin J et al. N Engl J Med 2015 (May 31). DOI: 10.1056/NEJMoa1504030

PFS in untreated melanoma

Combination of PD-1 and CTLA-4 blockade was more effective than either agent alone



Major Challenges for Combination Therapy

- Contribution of each component and related trial design issues
- Dose, schedule and sequencing of the agents combined
- Issues related to Intellectual property
- Toxicities can be substantial

Table 3. Adverse Events.*

Event	Nivolumab (N=313)		Nivolumab plus Ipilimumab (N=313)		Ipilimumab (N=311)	
	Any	Grade 3 or 4	Any	Grade 3 or 4	Any	Grade 3 or 4
	number of patients with event (percent)					
Any adverse event	311 (99.4)	136 (43.5)	312 (99.7)	215 (68.7)	308 (99.0)	173 (55.6)
Treatment-related adverse event†	257 (82.1)	51 (16.3)	299 (95.5)	172 (55.0)	268 (86.2)	85 (27.3)
Diarrhea	60 (19.2)	7 (2.2)	138 (44.1)	29 (9.3)	103 (33.1)	19 (6.1)
Fatigue	107 (34.2)	4 (1.3)	110 (35.1)	13 (4.2)	87 (28.0)	3 (1.0)

Biomarker Investigations

- Identify targets for immunotherapeutic agents
- Select and enrich patient population
- Correlate the prognostic marker with efficacy and / or safety
- Develop companion diagnostic test
- Part of precision medicine

Conclusion

- Cancer Immunotherapy has evolved tremendously since the last global regulatory summit in 2008.
- Novel and better science has been the driving force for this evolution.
- Many regulatory challenges exist, especially in the era of novel therapies and their combinations.
- Interaction and collaboration of stakeholders are key for future success.

CBER OCTGT DCEPT
Oncology Branch Members

Peter Bross, MD (Team Leader)	Bindu George, MD (Team Leader)	Ke Liu, MD, PhD
Chaohong Fan, MD, PhD	Ching-Hsien Lee, MD, PhD	Robert Sokolic, MD
Sadhana Kaul, MD	Maura O'Leary, MD	
Robert Le, MD, PhD	Lydia Martynec, MD	
Kristin Baird, MD	Kevin Shannon, MD	

Contact Information

Ke Liu, MD, PhD

Chief, Oncology Branch
Division of Clinical Evaluation, Pharmacology and Toxicology
Office of Cellular, Tissue and Gene Therapies
Center for Biologics Evaluation and Research
Food and Drug Administration

ke.liu@fda.hhs.gov

OCTGT Contact Information

- Regulatory Questions:
- Contact the Regulatory Management Staff in OCTGT at CBEROCTGTRMS@fda.hhs.gov or Lori.Tull@fda.hhs.gov
- OCTGT Learn Webinar Series: http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm

Public Access to CBER

CBER website:
http://www.fda.gov/BiologicsBloodVaccines/default.htm

Consumer Affairs Branch (CAB)
Email: ocod@fda.hhs.gov

Manufacturers Assistance & Technical Training Branch (MATTB)
Email: industry.biologics@fda.gov

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