Multiple Myeloma Update

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Outline

- Updates on existing/approved drugs for multiple myeloma
- Updates on new/upcoming drugs and strategies for multiple myeloma
- New strategies in development at Penn and elsewhere

Existing drugs for multiple myeloma

- **Chemotherapies**: melphalan, cyclophosphamide, Doxil, bendamustine, doxorubicin, cisplatin, etoposide
- **"-imids":** thalidomide (Thalomid), lenalidomide (Revlimid), pomalidomide (Pomalyst)
- **Proteasome inhibitors**: bortezomib (Velcade), carfilzomib (Kyprolis), **ixazomib (Ninlaro)**
- **HDAC inhibitors:** panobinostat (Farydak)
- **Monoclonal antibodies:** **daratumumab (Darzalex)**, **elotuzumab (Empliciti)**

Updates on existing drugs

- **Initial therapy updates**
  - Does choice of initial therapy matter for long-term outcomes?
  - Is combination of lenalidomide, bortezomib, and dexamethasone (RVD) better than lenalidomide and dexamethasone (RD) alone?
  - SWOG 0777 Study: long-term, randomized study to answer this question.
  - RVD seems to be better than RD for long-term outcomes in patients not receiving stem cell transplant.

Updates on existing drugs

- **Transplant updates**
  - Is transplant still useful with all these new drugs?
    - Palumbo NEJM 2014: transplant prolongs long-term survival
    - Palumbo ASH 2015 (separate study): transplant prolongs long-term survival
  - When should transplant be used? Early or delayed? (IFM-2009 study)
    - RVD initial therapy → randomize up-front vs. delayed ASCT.
    - Up-front ASCT:
      - More complete responses and "very good partial responses"
      - More patients achieved "MRD-negative"
      - Better time-to-progression
    - Still not sure about long-term survival

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Updates on existing drugs

- **Carfilzomib** (proteasome inhibitor, IV infusion)
  - Very effective alone and in combination with lenalidomide for relapsed disease (ASPIRE study, ENDEAVOR study)
  - Effective as weekly (at higher dose) rather than twice weekly infusion.
  - Effective as initial therapy with cyclophosphamide + dexamethasone (not yet a standard first-line therapy, studies ongoing)
  - Higher doses may be effective in patients who stopped responding to lower doses.

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Updates on existing drugs

- **Ixazomib** (proteasome inhibitor, oral)
  - Very recently FDA-approved in combination with lenalidomide and dexamethasone for relapsed multiple myeloma
  - Similar side-effect profile to bortezomib
  - Once-weekly dosing
  - Clinical trials ongoing for:
    - Initial therapy
    - Maintenance therapy (alone and in combination with lenalidomide)
- **Panobinostat** (HDAC inhibitor, oral)
  - FDA-approved with bortezomib
  - 20 mg dose safe/tolerable/effective with carfilzomib at 56 mg/m^2 dose

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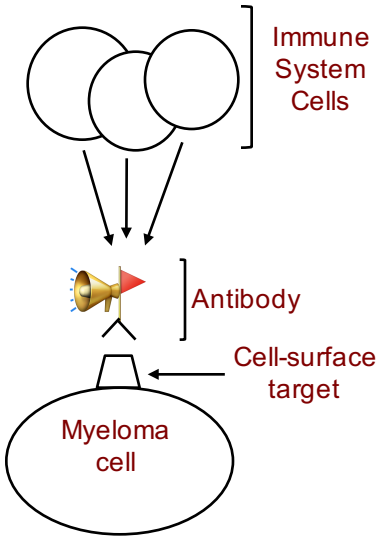
Updates on existing drugs

- **Daratumumab** (anti-CD38 antibody, weekly IV)
  - Recently FDA-approved as monotherapy for relapsed myeloma.
  - Promising combinations (pomalidomide, carfilzomib)
  - Clinical trials looking at use in initial therapy
- **Elotuzumab** (anti-CS1 antibody, weekly IV)
  - Recently FDA-approved with lenalidomide and dexamethasone
  - Increases response rate and possibly survival compared to lenalidomide alone
  - Many combinations being investigated



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New strategies

FDA-approved drugs

- Ibrutinib (BTK inhibitor, approved for lymphoma)
- Vemurafenib/Dabrafenib (BRAF inhibitors, approved for melanoma)
- Trametinib (MEK inhibitor, approved for melanoma)
- **Pembrolizumb, Nivolumab (PD-1 inhibitors)**

Not (yet) FDA-approved

- Ricolinostat (HDAC inhibitor, more specific than panobinostat)
- Isatuximab (anti-CD38 antibody, like daratumumab)
- Selinexor (XPO1 inhibitor)
- Filanesib (kinesin spindle protein inhibitor)
- ABT-199 (Bcl2 inhibitor)
- Dinaciclib (CDK inhibitor)
- **BET inhibitors**
- **BI-505 (anti-ICAM-1 antibody)**
- **CAR T cells**
- **BiTEs (anti-CD38, anti-BCMA)**
- **Vaccines and other immunotherapies**

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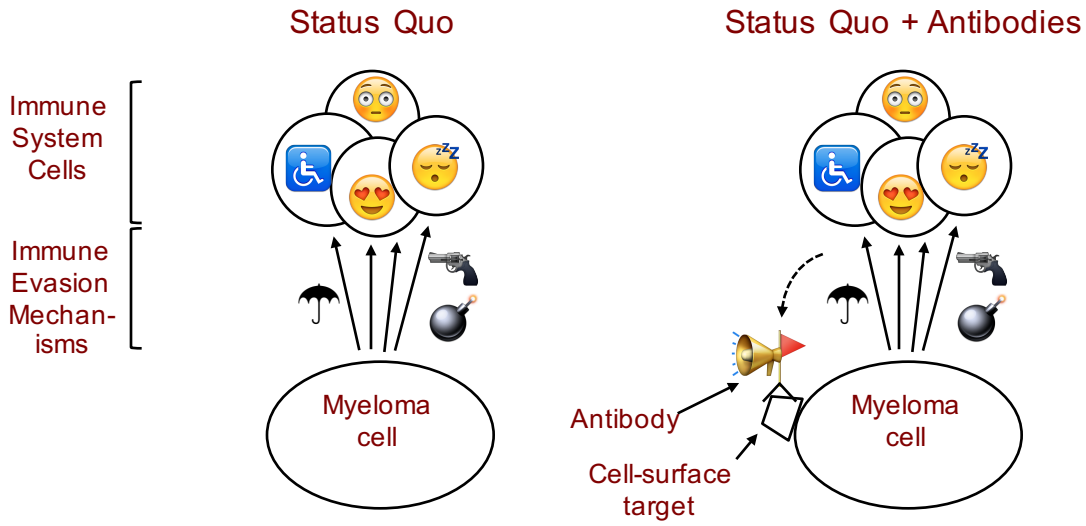
Immunotherapy strategies for myeloma



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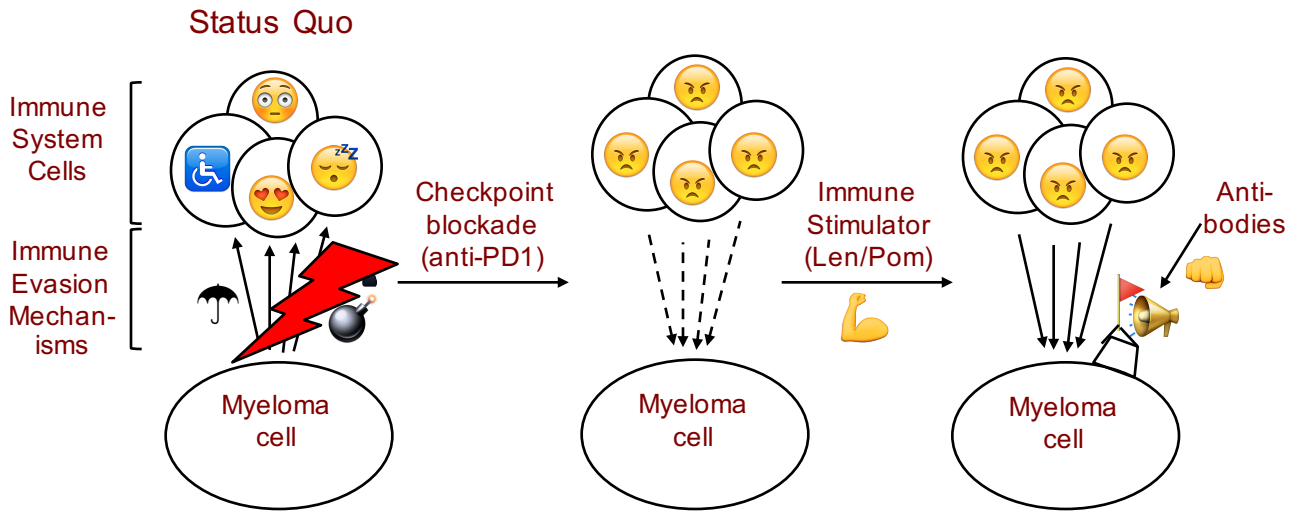
Immunotherapy strategies for myeloma



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Immune checkpoint blockade in myeloma

- Potential toxicities: inflammation of lung, liver, thyroid, bowels
- Single-agent nivolumab (BMS PD-1 inhibitor) was not very effective.
- Pembrolizumab (Keytruda): Merck PD-1 inhibitor
  - Two combination studies with lenalidomide/pomalidomide at ASH 2015
    - Safe
    - 50-75% response rates
  - Merck has a patient assistance program that may provide drug for free if insurance does not cover.

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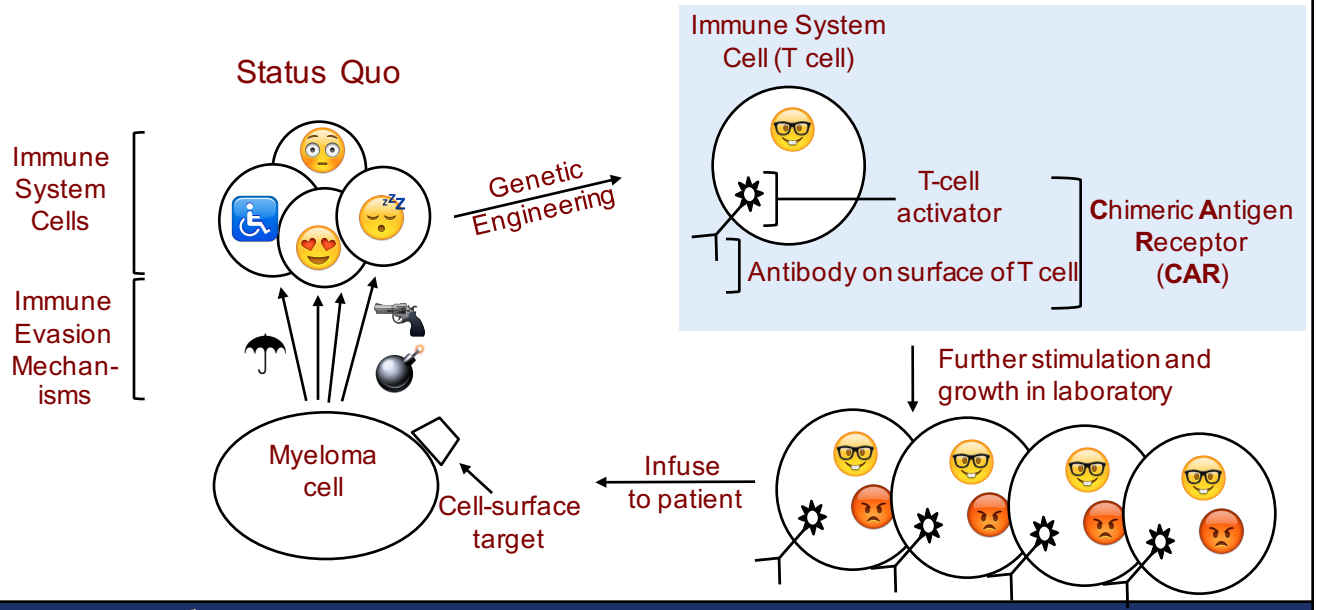
Immunotherapy strategies for myeloma – CAR T cells



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CAR T Cells for myeloma

- CARs against CD19 → impressive results in CLL, ALL, NHL
- Cell surface targets
  - CARs are more potent than antibodies – need more specific targets.
  - Candidate targets in multiple myeloma: BCMA, CS-1
  - CD19: Not on most myeloma cell, possibly on myeloma stem-cell
- ASH 2015: NCI study of anti-BCMA CAR T cells
  - Small, phase-1 study; multiple doses evaluated
  - 4/12 with responses, 1 VGPR and 1 sCR
  - Toxicities: cytokine release, neurotoxicity
- Phase 1 study of anti-BCMA CAR T cells ongoing at Penn (Dr. Adam Cohen)

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