mAbs to Empowered Antibodies - Strategies beyond IgG

A historical look at the development of monoclonal antibodies, today's success and products of the future

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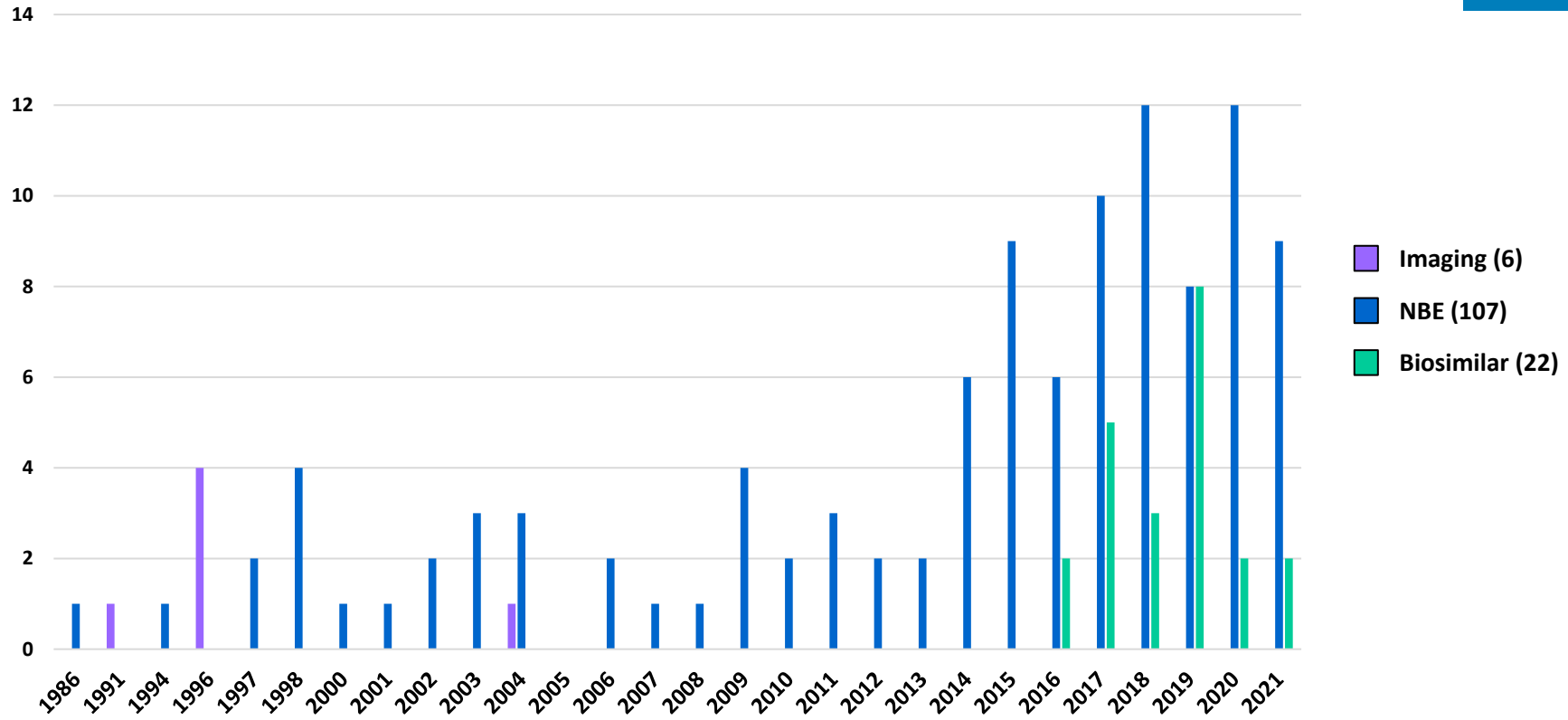
Disclaimer

- The views presented today do not represent official FDA policy, but rather represent my opinion based on my experience as a reviewer of monoclonal antibody and related products at the FDA.

mAb product approvals



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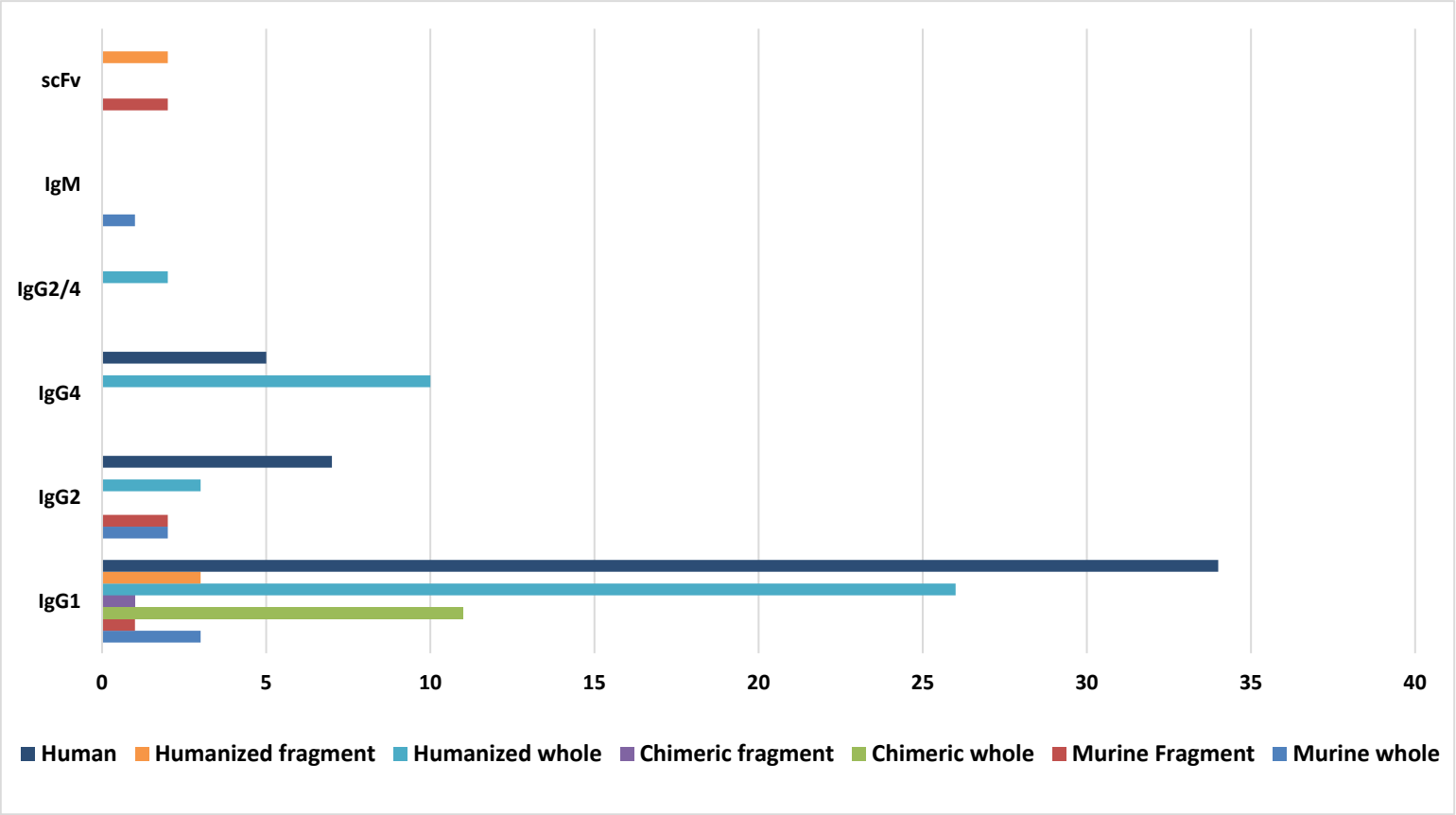


Historical Viewpoint of mAb Development

1980s Murine mAbs

- Immunogenic
- Short half life
- Limited effector function in humans

1990s V region engineered to reduce immunogenicity

- Chimeric
- Humanized
- Human

- ADCs were in clinical trials in the 1980s but used murine mAbs
- BsAbs were in clinical trials in the 1990s but manufacturing was inefficient (quadromas)

mAb Development in the 21st Century

Fc engineering to reduce or enhance effector function
- Specific mutations
- CH domain combinations
- Glycoengineering

mAb fragments
- sFv and variations
- Single domain mAbs and variations

Novel mAb Constructs (with or without Fc region)
- Bispecific
- Multispecific constructs
- Shuttle constructs (BsAb or Bifunctional)

Cocktails (2 or more)

mAb Development in the 21st Century

Conjugates
- ADCs
  - New payloads
  - New linkers
  - New conjugation strategies
  - Non-oncology indications
- Toxin conjugates
  - Bacterial
  - Plant
- Radioimmunoconjugates
  - α emitters
- Imaging agents
  - Radiolabels (PET tracers)
  - Fluorescent dyes

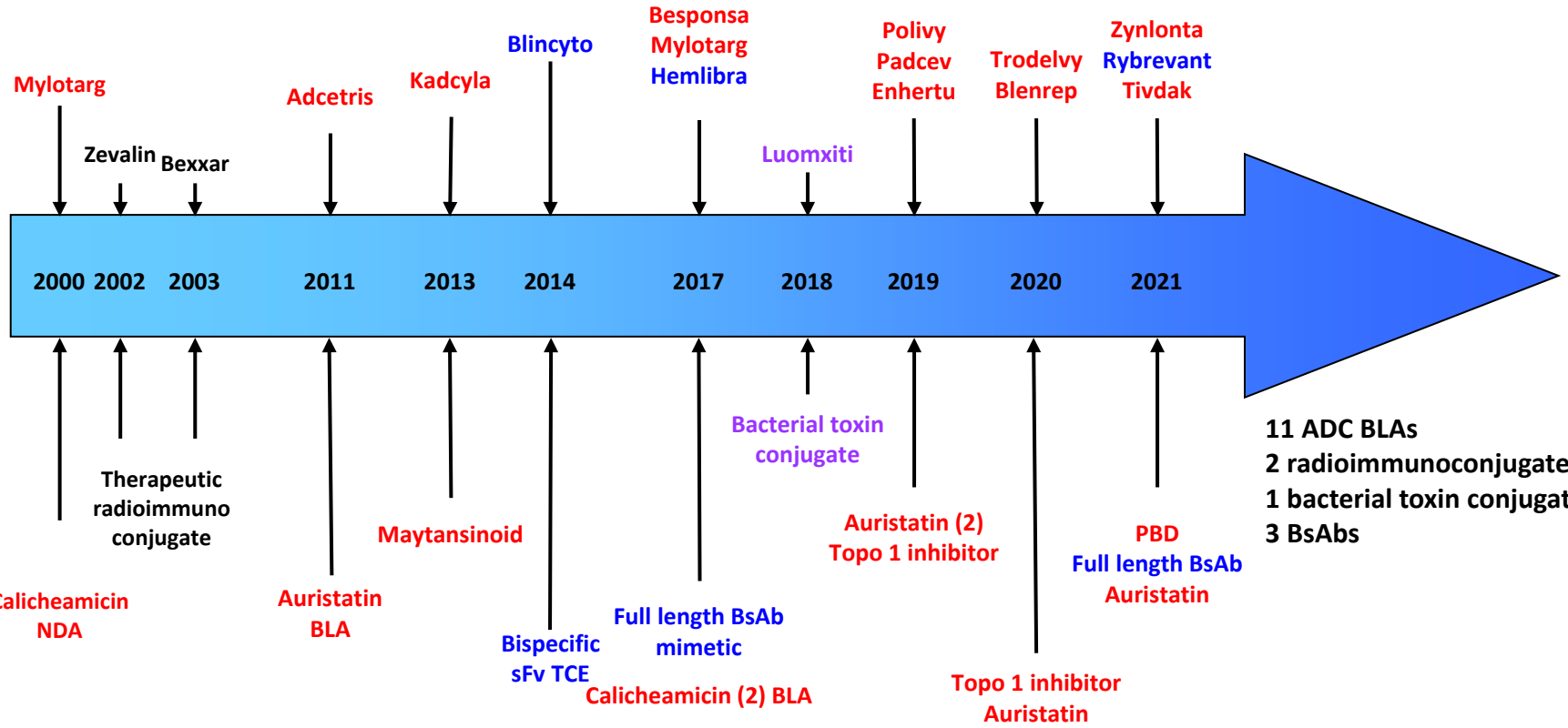
Bifunctional molecules
- Cytokines
- Cytokine receptors
- Hormones
- TCRs
- Other proteins/peptides

V region engineering to enhance PK

Non-IgG isotypes

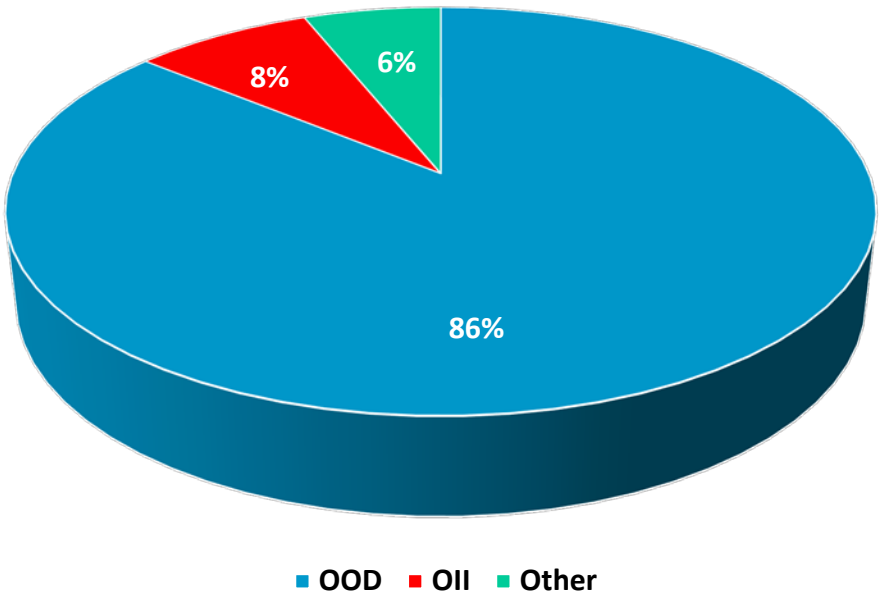
Combinations of different mAb constructs

Antibody Conjugate and BsAb Approvals

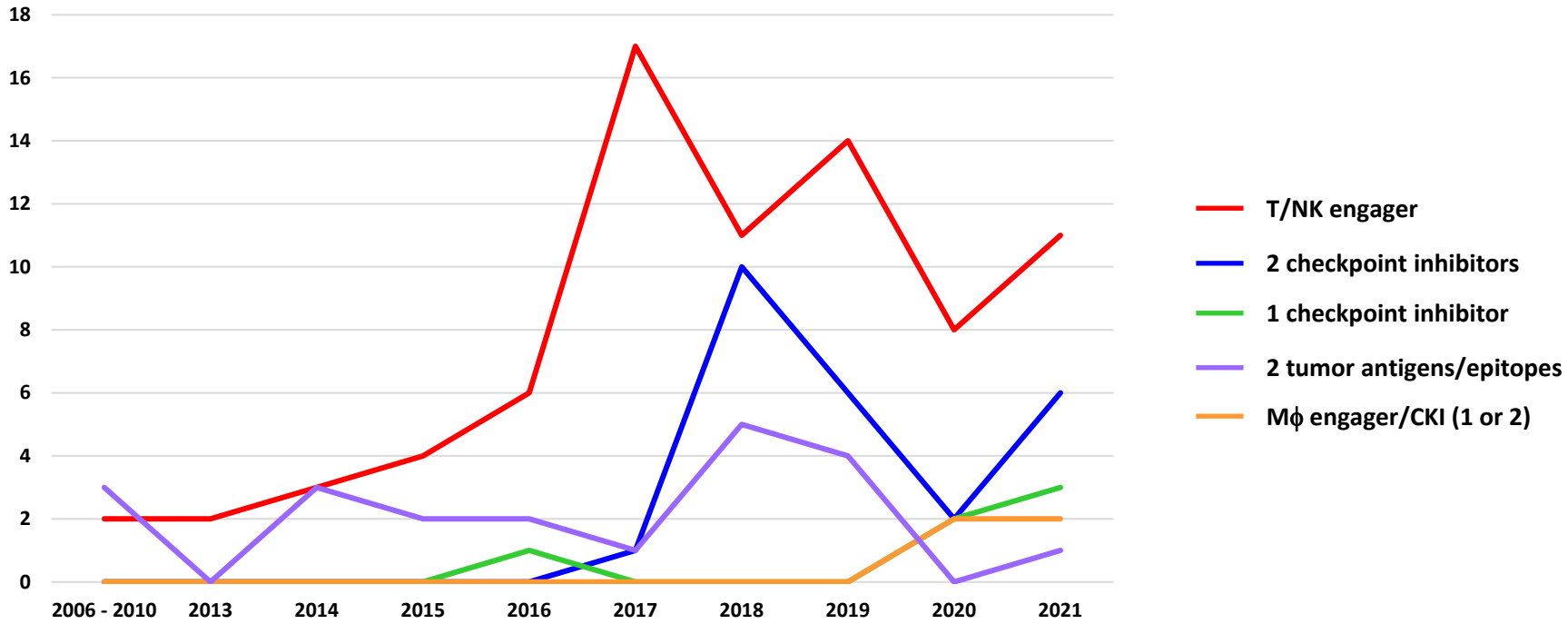


BsAb IND submissions 2006 - 2021

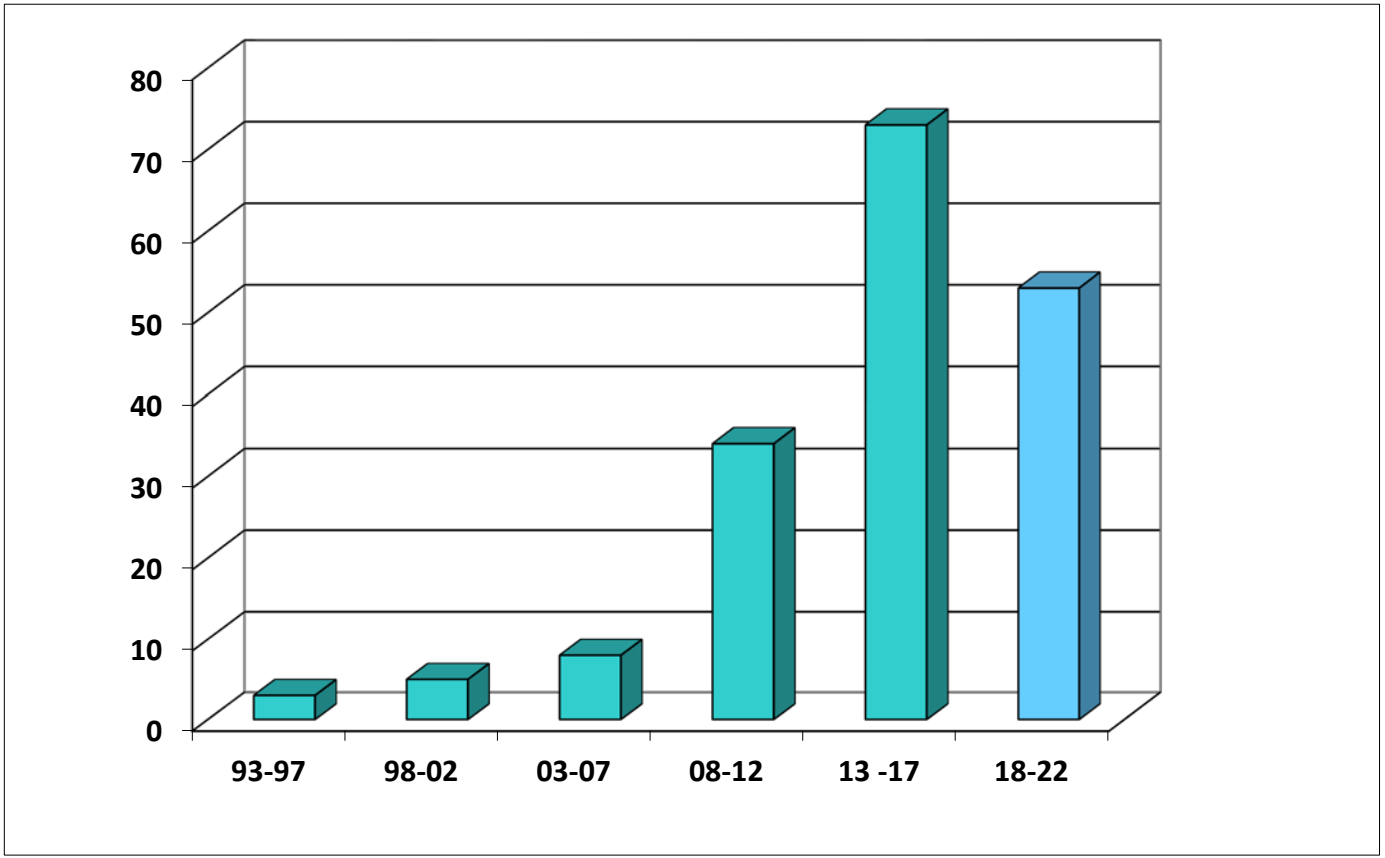
- There are >100 different BsAb formats
  - Most not in clinical studies
- scFv, nanobody, fragments
  - CH domain fusions, albumin, anti-albumin domains to extend half-life
- Intact IgG
- Intact IgG with appended V domains
- Different approaches for correct pairing of intact IgG constructs
- Asymmetric vs symmetric designs
- 1+1, 2+2, 1+2 arms



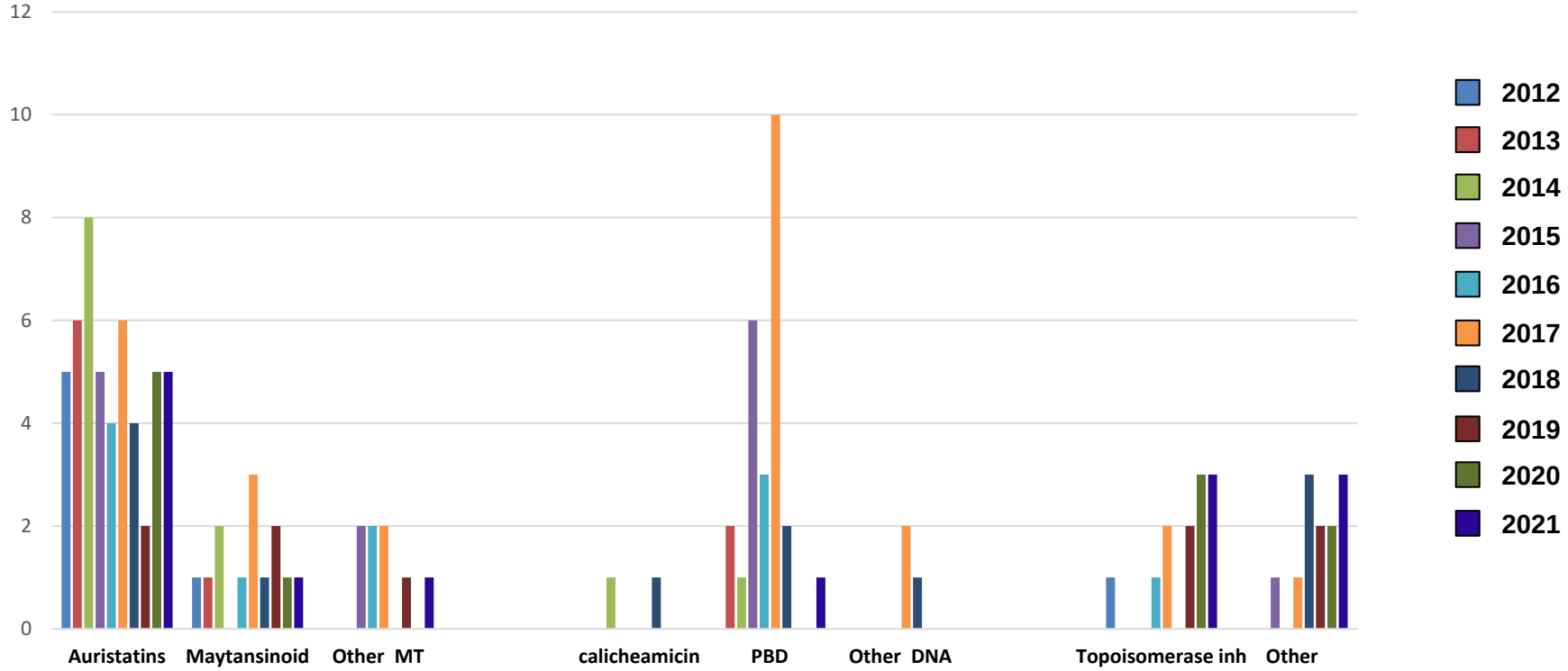
BsAb oncology submissions through 2021



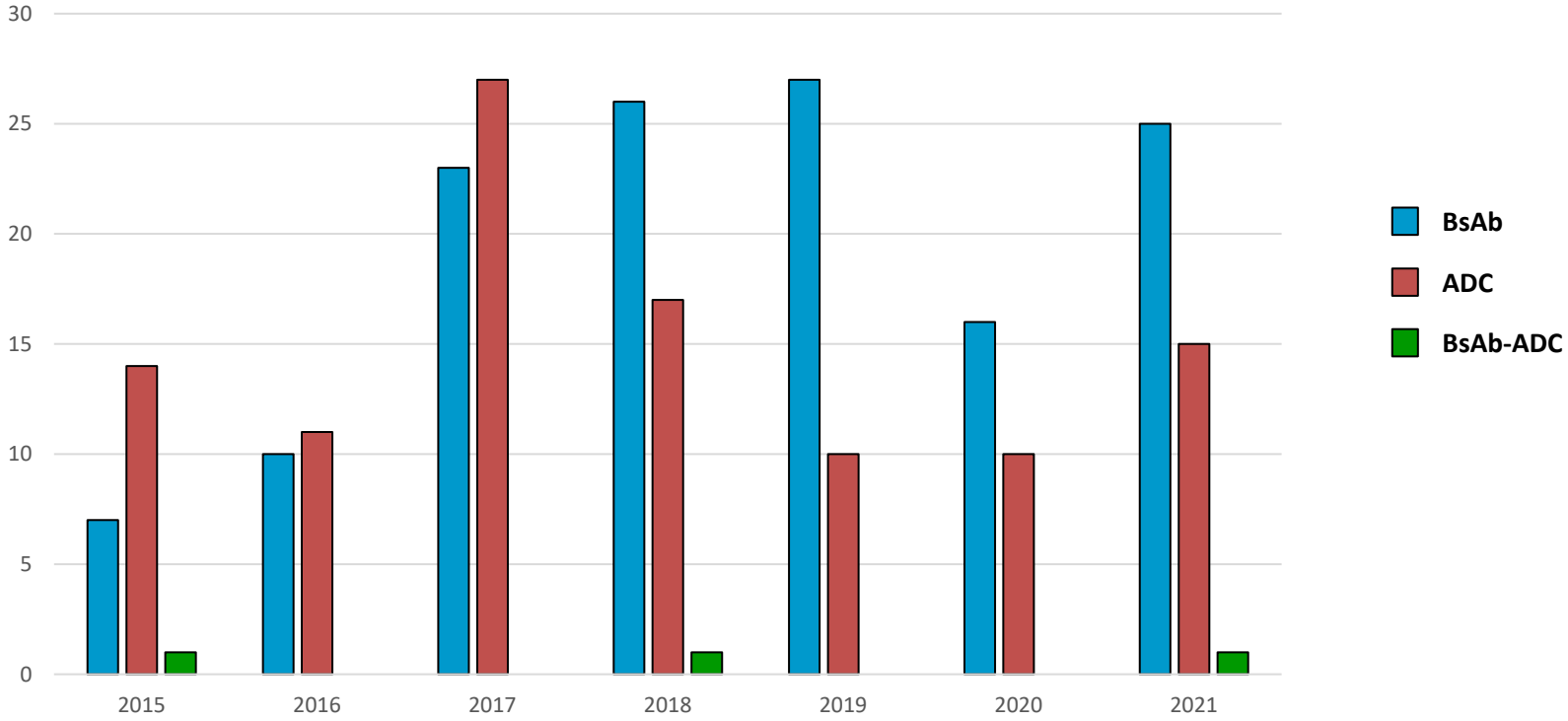
ADC IND submissions



ADC payload


12
10
8
6
4
2
0
Auristatins
Maytansinoid
Other MT
calicheamicin
PBD
Other DNA
Topoisomerase inh
Other
2012
2013
2014
2015
2016
2017
2018
2019
2020
2021

BsAb and ADC submissions 2015 - 2021



Future expectations

- IgG mAbs will have continued success (standard, glyco- or Fc-engineered)
- ADCs will have continued success
  - May see a lull as new targets, payloads, linkers, conjugation strategies and novel indications are developed
- BsAb approvals will start to catch up with ADCs
  - Too soon to know if certain designs (1+1 vs 1+2 for TCEs) will predominate
- It will be a while before we see bifunctional antibody approvals on a regular basis
  - Tebentafusp (scFv x TCR construct) is under review https://bit.ly/3sTdtwD
- Expect to see IgM, IgA/sIgA, and IgE mAbs
  - Few until start seeing success
    - Will need to develop an understanding of the CQAs
    - May see hybrid IgA/IgG and IgE/IgG constructs
    - MOv18 IgE anti-folate receptor α for advanced solid tumors (ovarian cancer) completed a Phase 1 study in 2020. Showed preliminary evidence of anti-tumor activity https://cancerres.aacrjournals.org/content/80/16_Supplement/CT141