# Evidence on the handling and administration of biological agents – An Update.

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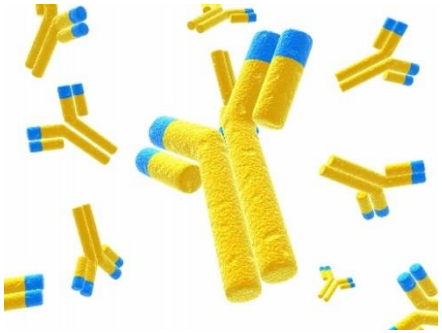
20TH March 2015

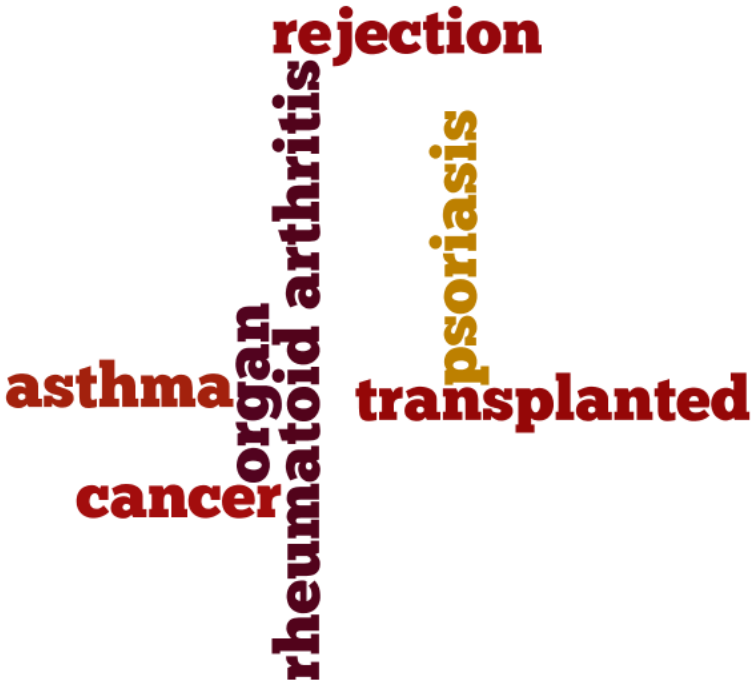
# Monoclonal antibodies - MABs

- Three type of MABs
  1. Completely murine origin (mouse or hamster protein)
     - - momab
  2. Chimeric (e.g. mouse + human)
     - - ximab *rituximab*
  3. Humanised
     - - zumab *trastruzumab*
  4. Human *adalimumab*



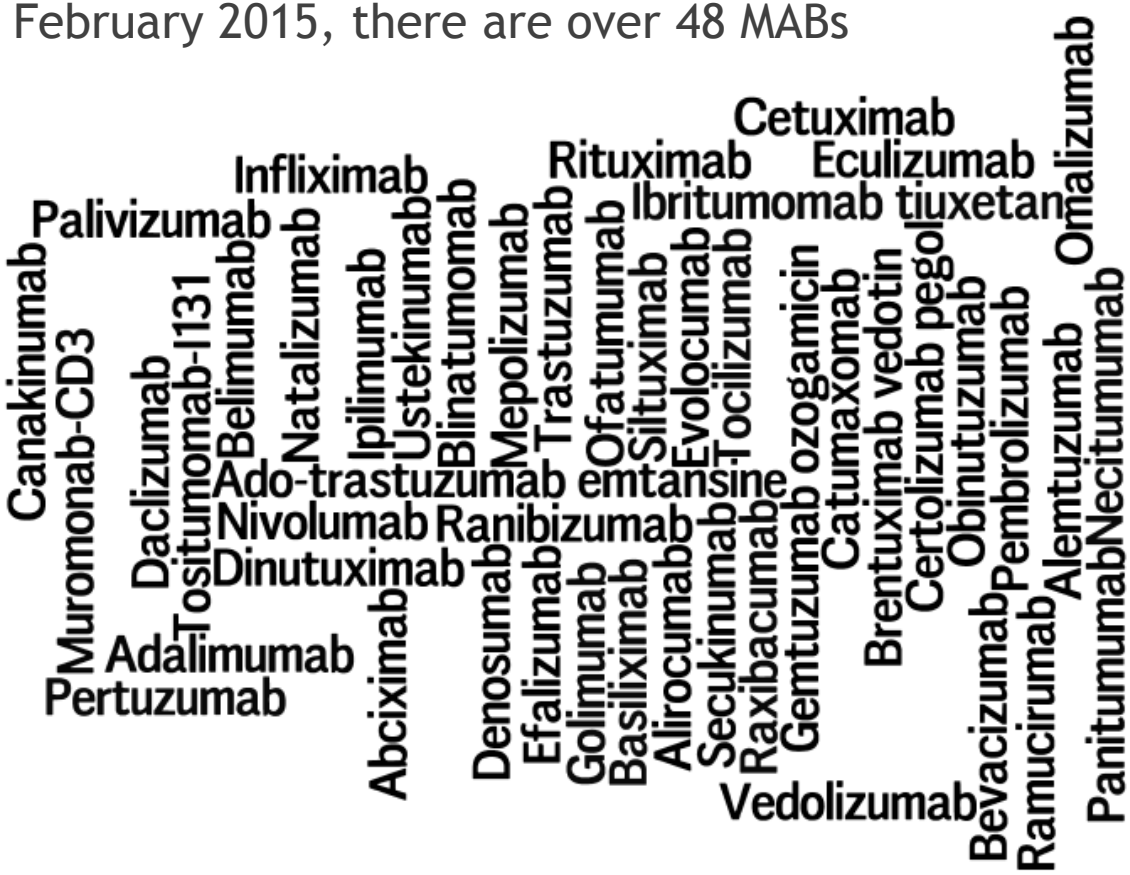
# NZ Funded MABs

- Abciximab
- Adalimumab
- Basiliximab
- Infliximab
- Natalizumab
- Rituximab
- Tociluzumab
- Trastuzumab



# European Union / FDA approved MABs

- As of February 2015, there are over 48 MABs




http://www.antibodysociety.org/news/approved_mabs.php

# Monoclonal Antibodies - A Hazardous Substance?

- National Institute for Occupational Safety and Health (NIOSH) 2014
- Criteria for being a hazard
  - Carcinogenic
  - Teratogenic or other developmental toxicity
  - Reproductive toxicity
  - Organ toxicity at low doses
  - Genotoxicity
  - Structure and toxicity profiles that mimic existing hazardous drugs

MABs are NOT cytotoxic

Unless used with cytotoxic agents / radioisotopes

# What are the risks?

- Formation of neutralising antibodies, provoking allergies, anaphylaxis or serum sickness
- Loss of clinical response
- Cross-reaction with endogenous proteins with vital biological function
- Enhancement of immune system activity leading to cytokine storm / systemic inflammatory response syndrome

wcmics WESTERN & CENTRAL MELBOURNE INTEGRATED CANCER SERVICE

Australian consensus guidelines for the safe handling of monoclonal antibodies for cancer treatment by healthcare personnel

Surveyed the following recipients:

- Oncology pharmacists, medical oncologists, haematologists and senior nursing staff
- Cancer Nurses Society of Australia
- Clinical Oncological Society of Australia
- Haematological Society of Australia and New Zealand
- Medical Oncology Group of Australia
- Society of Hospital Pharmacists of Australia

# Occupational Health and Safety Risk

Risk factors

- **1. Internal Exposure Risk**
  - Dermal absorption
  - Inhalation absorption
  - Mucosal absorption
  - Oral absorption
- **2. Toxicity**
  - Cytotoxicity
  - Carcinogenicity
  - Genotoxicity or mutagenicity
  - Teratogenicity or developmental toxicities
  - Organ toxicity at low doses
  - Immunogenicity

# Dermal Absorption

- MABs are large protein molecules

  ~147-153 kilo Daltons

- Too big compared to topical or transdermal drug delivery, typically < 500 Daltons

- → Dermal absorption generally considered to be <u>unlikely</u>

- All MABs (with similar physiochemical properties) considered no different to other pharmaceutical products containing commonly used excipients

# Absorption following Inhalation

- Local and systemic absorption of MABs via inhalation of aerosolised formulations has been demonstrated in animal models.

- Estimates on the bioavailability of high molecular weight substances have been at 5% by inhalation.

- → Staff may be exposed to powdered or aerosolised liquid particles during preparation of doses. Potentially viable route of internalisation.

# Mucosal Absorption

- Local and system absorption of MABs has been demonstrated in animal models.
- Given the size of MABs, intranasal absorption is possible.
- → Staff may be exposed to powdered or aerosolised liquid particles.

# Oral Absorption

- Protein nature susceptible to gastric acids and enzymes
- Studies have found *some* MABs being able to survive gastric enzyme and retain biological activity
- → Hand to mouth contamination is most likely scenario. Potentially viable route of internalisation with indeterminate effects.

# Cytotoxicity

- Not considered cytotoxic unless conjugated to cytotoxic agent
- → Immune-mediated cytotoxicity is explicitly different to the direct cytotoxic action of traditional anticancer agents

# Carcinogenicity

- Some MABs may increase the risk of lymphoma and other malignancies during therapeutic use
- → Potentially carcinogenic at *therapeutic* doses with unknown long term low dose exposure effects

# Genotoxicity / Mutagenicity

- MABs do not interact directly with DNA, thus not genotoxic.
- → MABs are considered neither genotoxic nor mutagenic

# Teratogenic

- No evidence of teratogenicity associated with occupational exposure to MABs.
- → Unknown long term low dose effects

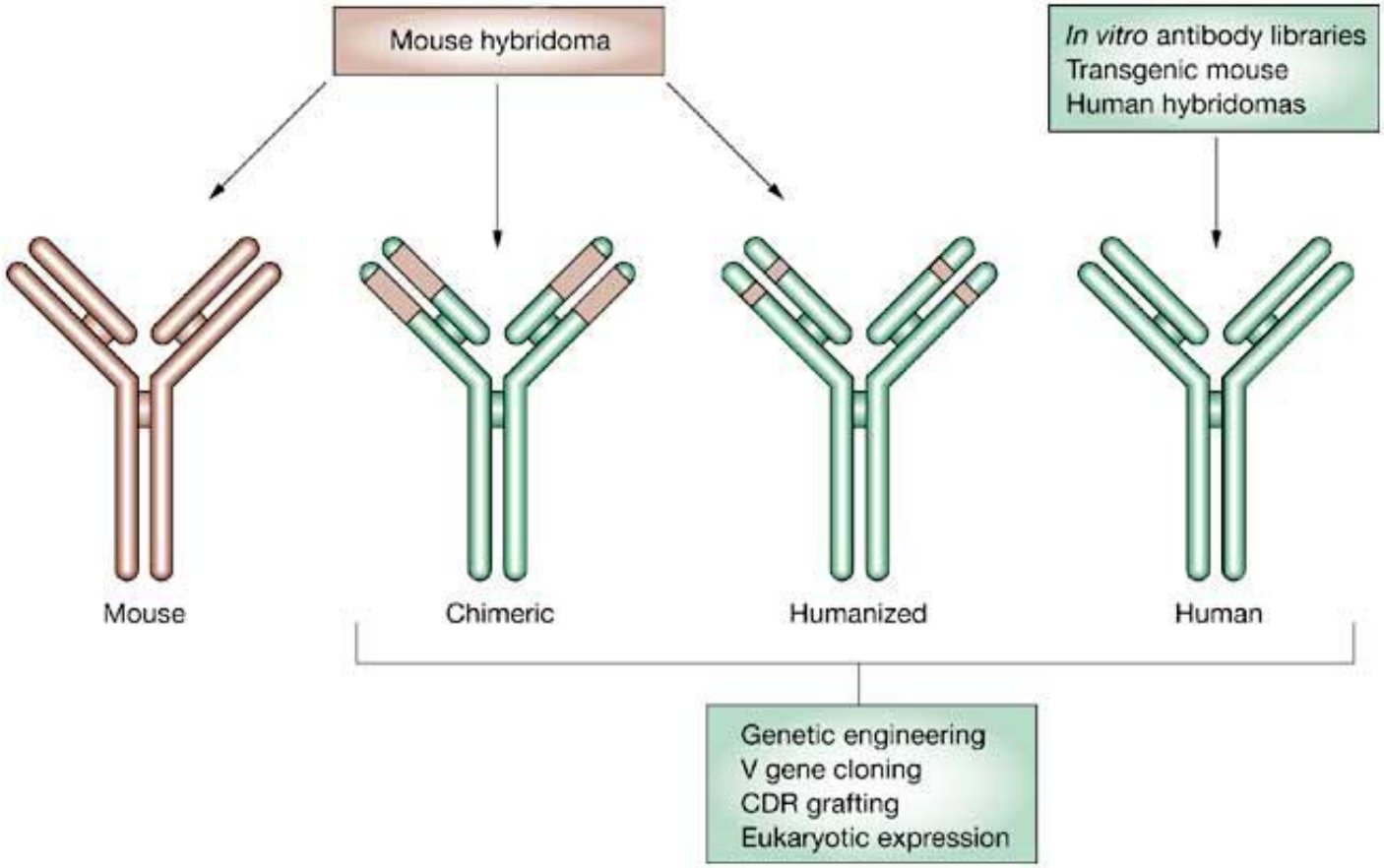
# Organ toxicity at low doses

- No evidence of organ toxicity from sub-therapeutic doses

# Immunogenicity

- MAB-induced immunogenicity is plausible and has been demonstrated with infliximab
- → Immunogenicity may occur at therapeutic exposures but unknown long term low dose effects

# Monoclonal Antibodies



# Manufacturer handling recommendations

**Table 5 - Manufacturer handling recommendations for pregnant personnel**

| Drug | Handling Recommendations | Formulation |
|---|---|---|
| Alemtuzumab | Avoid if pregnant or planning pregnancy | Solution |
| Bevacizumab*, Cetuximab*, Denosumab*, Ipilimumab*, Ofatumumab*, Panitumumab*, Rituximab* | No information available | Solution |
| Trastuzumab* | No information available | Powder |
| Brentuximab Vedotin*, Trastuzumab-Emtansine* | As per procedures for anticancer drugs | Powder |

*Teratogenic or developmental toxicities at therapeutic (or higher) doses in animal or human studies. Refer to appendix I for citations; manufacturer material safety data sheets and product information sheets.

# Recommendations – Available Safety Interventions


Preparation only

Not necessary for administration

# Recommendation – for Preparation

- Asceptic technique VS. sterile room
- Isolator Cabinet – not required
- Cytotoxic drug safety cabinets – not required
- Closed system drug transfer device – not required, but can reduce operator exposure and product contamination

- Preparation should occur in a dedicated area away from patients and carers

# So what does it mean?

- Nurses can make it on the ward!
- Pharmacy doesn't need to prepare it!
- Easier access!

# Operational and Clinical Factors

- Vial sharing
  - MABs are intended for single use-vials
  - Increases risk of microbial contamination
  - No different to other parenteral medicines
- Complexity of preparation
  - Increased preparation steps → increased manufacturing error, occupational exposure, and/or microbial contamination
  - Most MABs require between 2 to 8 manufacturing steps
  - Proteins easily broken down with excessive shaking
  - → Require experienced and well trained staff; centralised manufacturing location eg pharmacy cleanroom

# Operational and Clinical Factors

- Medication error
  - High risk (and expensive) drugs
  - Multiple strengths available, possibly accidental product selection error
  - ➔ As with other medications, can be done on the ward with well trained staff, but best achieved and monitored in centralised manufacturing location
- Cost efficient
  - Achieve best value for money, within the constraints of Good Manufacturing Practice

# Handling recommendations based on risk

**Table 7 – Exposure Risk**

| Risk Matrix | | Risk of internalisation | | | |
|---|---|---|---|---|---|
| | | None | Low | Moderate | High |
| **Likelihood of Exposure** | Unlikely | | Oral | Inhalation* Mucosal* | |
| | Possible | | | Inhalation** Mucosal** | |
| | Likely | Dermal | | | |

*Limited to administration process

**Limited to preparation of doses for administration

**Table 8 - Recommended handling precautions based on exposure risk**

| Exposure Risk | Recommended Handling Precaution |
|---|---|
| **No / Low Risk** | No additional precautions required, standard operating procedures for both the preparation of doses for administration and administration. |
| **Moderate Risk** | No additional precautions required, standard operating procedures for administration. Protective mask and eyewear, in addition to standard operating procedures for the preparation of doses for administration. |
| **High Risk** | Treat like a cytotoxic or hazardous substance for both the preparation of doses for administration and administration. |

*Standard Operating Procedures: standard operating procedure for parenterally administered pharmaceutical agents (i.e. aseptic technique according to the Australian Commission on Safety and Quality in Healthcare[53]).

# So what now?

- Australian Consensus Guideline endorsed by:
  - Association of Hospital Pharmacists
  - Cancer Nurses Society of Australia
  - Clinical Oncology Society of Australia (COSA)
  - COSA Cancer Pharmacists Group
  - Medical Oncology Group of Australia
  - Pharmacy Guild of Australia
  - Society of Hospital Pharmacists of Australia
- New Zealand Guideline
  - Aware of Australian guideline, multiple oncology pharmacists and hospital pharmacies interested in forming a committee to discuss this evidence and form a national approach
  - Involvement of other professional bodies

# Summary

- Preparation of MABs
  - Gloves advised for asceptic technique
  - Use mask, gown and eye protection
  - Experienced and well trained staff
  - Centralised pharmacy is ideal
- Administration of MABs
  - Treat similarly to other intravenous medications
  - Gloves and gown not necessary
  - Masks may be used when dis/connecting IV MABs
  - Dispose of in regular waste

**Follow local protocols**

# Questions

# References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