Monoclonal Antibody
Inject mouse with antigen X

- Mutant mouse myeloma cells unable to grow in HAT medium
- Mouse spleen cells; some cells (red) make antibody to antigen X

1. Mix and fuse cells
Mix and fuse cells

Transfer to HAT medium

Unfused cells ( ) die
Fused cells ( ) grow
Unfused cells (○ ○ ● ●) die
Fused cells (● ● ●) grow

3. Culture single cells in separate wells

Test each well for antibody to antigen X
De novo synthesis of purine nucleotides
PRPP (5-Phosphoribosyl-1-pyrophosphate)

Blocked by antifolates
CHO from tetrahydrofolate

Blocked by antifolates
CHO from tetrahydrofolate

De novo synthesis of TMP
Deoxyuridylate (dUMP)

Blocked by antifolates
CH$_3$ from tetrahydrofolate

Nucleic acids
Guanylate (GMP) → Inosinate (IMP) → Adenylate (AMP) → Nucleic acids

Guanine
Hypoxanthine
Adenine

Salvage pathways

TK (thymidine kinase)
Monoclonal Antibodies for Therapy

- Receptor CD-3
- Receptor CD-4
- Receptor CD-25
- Receptor CD-40
- Receptor IL-2
- Receptor TNF

The high specificity of these antibodies improves selectivity and reduces toxicity of the therapy and alters the disease course in several different autoimmune disorders.
Muromonab-CD3 (OKT3)

Directed against the CD3 molecule on the surface of human thymocytes and mature T-cells can also be useful in the treatment of renal transplant rejection.

In vitro, muromonab-CD3 blocks killing by cytotoxic human T cells and several other T-cell functions.
Antitumor MABs
Alemtuzumab

- Humanized IgG1 with a kappa chain that binds to CD52 found on normal and malignant B and T lymphocytes, NK cells, monocytes, macrophages and a small population of granulocytes.
- Currently alemtuzumab is approved for the treatment of B-cell chronic lymphocytic leukemia in patients who have been treated with alkylating agents and have failed fludarabin therapy.
Bevacizumab

- Is a humanized IgG1 monoclonal antibody that binds to VEGF and inhibits VEGF from binding to its receptor, especially on endothelial cells.
- Antiangiogenic, inhibit growth of blood vessels (angiogenesis)
- Approved for first line treatment of patients with metastatic colorectal cancer alone or in combination with 5-FU-based chemotherapy
Cetuximab

• Targets epidermal growth factor receptor (EGFR)
• Decreases in kinase activity, matrix metalloproteinase activity, growth factor production, increased apoptosis.
• For use in patients with metastatic colorectal cancer, whose tumors overexpress EGFR.
• Alone or in combination with Irinotecan
Rituximab

• Binds to the CD20 molecule on normal and malignant B lymphocytes.
• For the therapy of B-cell non Hodgkin Lymphoma.
• Mechanism of action: complement-mediated lysis, ADCC and induction of apoptosis in the malignant.
• Synergistic with chemotherapy (fludarabine, CHOP) for lymphoma.
Trastuzumab

• Binds to extracellular domain of the human epidermal growth factor receptor HER-2/neu.
• This antibody blocks the natural ligand from binding and down-regulates the receptor.
• For the treatment of metastatic breast cancer in patients whose tumors overexpress HER-2/neu.
MABs Used to Deliver Isotopes to Tumors
Arcitumomab

- Murine F(abb’)₂ fragment from an anti-carcinoembryonic antigen (CEA) antibody labeled with technetium 99m (⁹⁹ᵐTc) that is used for imaging patients with metastatic colorectal carcinoma (immunoscintraphy) to determine extent of disease.

- CEA is often upregulated on tumor in patients with gastrointestinal carcinomas.
Capromab Pendetide

• Murine monoclonal antibody specific for prostate specific membrane antigen.
• It is coupled to isotopic indium ($^{111}$In) and is used in immunoscintigraphy for patients with biopsy-confirmed prostate cancer and post-prostatectomy
Ibritumomab tiuxetan

- An anti-CD20 murine monoclonal antibody labeled with isotopic yttrium (\(^{90}\text{Y}\)).
- For follicular or B-cell non Hodgkin Lymphoma
Tositumomab

• Another anti-CD20 monoclonal antibody and is complexed with iodine 131 ($^{131}$I).
• Follicular Non-Hodgkin lymphoma
• Toxicities: thrombocytopenia and neutropenia.
MABs Used as Immunosuppressant and Anti-Inflammatory Agents
Anti-TNF-Alpha MABs

blocks interaction of TNF-alpha proinflammatory cytokine, with TNF-receptors on cell surface = suppression of downstream inflammatory cytokines such as IL-1 and IL-6 and adhesion molecules involved in leukocyte activation and migration.

Increased risk of lymphoma
- Adalimumab
- Etanercept
- Infliximab
Basiliximab

- Binds to CD25, the IL-2 receptor alpha chain on activated lymphocytes
- IL-2 antagonist, blocking IL-2 from binding to activated lymphocytes (immunosuppressant)
- For prophylaxis of acute rejection in renal transplant patients
Omalizumab

- Anti-IgE recombinant humanized monoclonal antibody
- For treatment of allergic asthma in adult patients
- Blocks the binding of IgE to high affinity FcεR on basophils and mast cells, which suppresses IgE-mediated release of type I allergy mediators, such as histamine and leukotrienes
Abciximab

• Fab fragment of a murine-human monoclonal antibody that binds to the integrin GPIIb/IIIa receptor on activated platelets and inhibits fibrinogen, von Willebrand factor and other adhesion molecules, from binding to activated platelets, thus preventing their aggregation.