The future: complex proteins and targeted therapies

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Biologics

- Medicinal products
- Created by biologic processes
- Not chemically synthesized
- Can be
  - Vaccines
  - Viruses
  - Gene therapy
  - Blood or blood components
  - Stem cells, immune cells, tissue or organs
  - Recombinant therapeutic proteins (main group for new drugs)
Oncolytic virotherapy

- In 1971, Lancet published a case report of a child whose Burkitt’s Lymphoma resolved when he contracted measles
- Live viruses as a treatment for cancer
- Opportunistic pathogens that selectively enter cancer cells and replicate
- Cell lysis results in release of tumour antigens to trigger the host’s immune system
- Virus must be safe, replication competent, genetically engineer-able, commercially viable
1. Binding to CAR and integrin

TARGET CELL

2. Internalization

CYTOPLASM

3. Vesicular transport

4. Endosomal escape

5. Release of viral DNA

NUCLEAR PORE

6. Viral transgene expression

NUCLEUS
Oncolytic virotherapy

- Recombinant Human Adenovirus Type 5 (Oncorine® - Shanhai Sunway Biotec) approved for head and neck cancers
- Oncolytic herpes simplex virus -1 + GM-CSF (OncoVEX® - Amgen) in Phase 3 for melanoma and head and neck tumours
- Cocksackie virus A21 (Cavatak® - Viralytics) in Phase 2 (including in Australia) for metastatic melanoma and gliomas
Immune therapeutics

- The incidence of several cancers are high in immuno-suppressed patients
- The immune system has an important protective role in protecting the body from cancer cells
- First example
  - Live attenuated Mycobacterium Bovis (BCG) bladder washout to treat localised bladder cancer (Immucyst®, Oncotice®)
Immune therapeutics

- Sipuleucel-T (Provenge®) for prostate cancer
- Only product approved by FDA
- Autologous cellular immunotherapy
- Described as a therapeutic cancer vaccine
- Manufactured for individual patients using their own immune cells
- Patient’s own white cells extracted via leukapheresis
- Primarily dendritic antigen presenting cells (APC’s) are separated and utilised
Immune therapies

- Incubated with a fusion protein with 2 parts
  - Prostatic acid phosphatase antigen (PAP - present in 95% of prostate cancer cells)
  - GM-CSF (to assist in maturation of APC’s)
- Activated immune cells are re-infused back into the patient
- Initiate a T-cell mediated immune response against cancer cells carrying the PAP antigen
- Survival benefit demonstrated in clinical trials
- Further investigation and development
PROVENGE ACTIVATES IMMUNE CELLS

Resting immune cell → Activated immune cells multiply → ...and attack prostate cancer
Therapeutic antibodies

- Not a new modality in medicine
- Polyclonal antiserums used for over 50 years
- Specific antibodies developed in 1970’s and still used today (immunoglobulins for hepatitis, tetanus, rabies, anti-serums, gammaglobulin)
- Took until 2000’s to successfully generate antibody mediated drugs
- Still use similar products in therapeutics today
  - Antithymocyte globulin (equine or rabbit ATG) in non-matched bone marrow transplant to prevent GVHD
Recombinant therapeutic proteins

- Composed of sugars, amino acids, proteins, nucleic acids or combinations of these
- Now most commonly produced by biotechnology methods using DNA recombinant technology
- Extremely complex molecules and proteins with multiple physical presentations
- Most new drugs now and in the future are “biologics” rather than “small” molecules
- Provide targeted therapy with high affinity, binding selectivity and specificity, narrow toxicity profile, long half lives
Recombinant therapeutic proteins

- Limitations include:
  - unwanted immune responses,
  - poor tissue penetration and oral bioavailability,
  - difficult to produce and formulate,
  - expensive,
  - how to handle in terms of compounding in Pharmacy

- Profound impact in many fields of medicine

- Provide targeted treatments in diseases where previously there were no treatments
Recombinant therapeutic proteins

- Primarily in oncology, inflammatory diseases and disorders of the immune system (rheumatology, dermatology, nephrology, immunology, neurology)
- In general, limited side effect profiles (most common - injection site reactions; rare - hypersensitivity, immunogenicity)
- Initial concerns over increases in infections, malignancies, lymphoproliferative disorders
- However, extremely expensive in comparison to standard therapy (from $10K - $100K per annum)
Recombinant DNA products

Fall into 3 categories

1. Products identical to the body’s own signalling proteins

2. Monoclonal antibodies (mAbs)
   - Secreted from a single B cell (cell line), all of which recognise only one epitope of the antigen
     1. Mouse (suffix –omab)
     2. Chimeric mouse / human (suffix –ximab)
     3. Humanised (suffix –zumab)
     4. Fully Human (suffix –umab)

3. Receptor constructs or fusion proteins
1. Signalling proteins

- The first of the biologics
  - Human insulins (Eli Lilly, NovoNordisk) for diabetes
  - Interferons (Roche, Schering Plough) then peginterferons for hepatitis B and C
  - Human growth hormone
  - Erythropoiesis factors
  - Granulocyte colony stimulating factors (g-CSF)
a. Erythropoiesis factors

- Used for chronic anaemia in patients with end stage renal failure
  - Epoetin alpha (initiator product in Australia) - Eprex® - Janssen. S100 funded. Dosed three times per week. Ave cost $11K per year
  - Darbepoetin - Aranesp® - Amgen. S100 funded. Dose every fortnight. Ave cost $15K per year
  - Methoxy polyethylene glycol epoein beta (pegulated epoetin beta) – Mircera® – Roche. S100 funded. Dose once a month. Ave cost $12K per year

- Off label use (non-PBS reimbursed) – Jehovah's witnesses, inpatients, anaemia of other causes (eg. malignancy, cardiology)
Biosimilars (similar biological medicinal products, subsequent entry biologics)

- Small molecule drugs can be chemically synthesised to be identical (generics)
- Because biologics require DNA recombinant technology using specific cell-derived manufacture, identical proteins can only come from the exact same cell-line
- Therefore, subsequent “generic” biologics (made from a similar but different cell line) can only be considered as similar, not identical, and therefore, are not substitutable in therapy
First biosimilars - epoetin

1. Epoetin Beta (Neorecormon® - Roche). S100 funded. Similar to epoetin alpha.
2. Epoetin Lambda (Novicrit® - Novartis). S100 funded. Similar to epoetin alpha.

- Some hospitals to tender for EPO’s
- Significant price reductions (50% or more)
b. G-CSF’s

- Used to prevent severe neutropenia associated with chemotherapy
  - Filgrastim (Neupogen® - Amgen). S100 funded. Multiple doses per course. Approx $200 per dose.
  - Lenograstim (Granocyte® - Ipsen now Hospira). S100 funded. Similar cost
  - Pegulated filgrastim (Neulasta® - Amgen). S100 funded. Single dose per course. Approx cost $2000 per dose
Second biosimilars – g-CSF

- Filgrastim (Nivestim® - Hospira). S100 funded. Similar to Neupogen®
- Called filgrastim
- Significant discounts being offered to hospitals switching to the alternative product (between 35-50%)
2. Monoclonal antibodies

- Similar to natural human antibodies produced by the immune system to fight infections due to bacteria or viruses
- These are “custom-designed” to block or counteract specific substances in the body or to target specific cell types
- Usually aimed at pro-inflammatory proteins, specific immune-mediated cells or identified disease-causing patho-physiological targets
Chimeric monoclonal antibodies

- The first engineered therapeutic antibody drugs were mouse / human chimeric antibodies
- Infliximab (Remicade® - Schering Plough)
- Monoclonal antibody that specifically targets Tumor Necrosis Factor TNFα (pro-inflammatory cytokine).
- TNF is primarily responsible for a range of chronic autoimmune inflammatory conditions
Structure of Infliximab (cA2)

- Chimeric (mouse/human) IgG₁ monoclonal antibody
- Binds to TNFα with high affinity and specificity
Rendering TNF Biologically Inactive

Infliximab

- Monoclonal antibody (MAb)
- Anti-TNF
- TNF
- Target cell
- Macrophage

Etanercept

- Soluble TNF receptor
- TNF
- Target cell
- Macrophage
Infliximab

- PBS (CAR) funded for:
  - Crohn’s disease (CD), Fistulising Crohn’s disease (FCD), Rheumatoid arthritis (RA), Ankylosing spondylitis (AS), Psoriatic arthritis (PA), Severe chronic plaque psoriasis (PP)
- Cost between $3-4K per dose dependent on patient weight
- Approx 8 doses per year ($30K per patient per year)
Humanised monoclonal antibodies

- Mouse protein binding sites fragments grafted to human antibodies
- Humanised range of monoclonal agents
  - Bevacizumab (Avastin® - Roche) anti-VEGF (vascular endothelial growth factor) for metastatic colorectal cancer
  - Trastuzumab (Herceptin® - Roche) for HER2 (human epidermal growth factor receptor) positive breast cancer
  - Natalizumab (Tysabri® - Biogen-Idec) anti-alpha-4-integrin cell adhesion molecule for MS
Fully human Monoclonal Antibodies

- Genotype / phenotype packaging
- Advanced chemical engineering
- Fully human agents with no foreign protein involved
- First was
  - Adalimumab (Humira® - Abbott) anti-TNFα for RA, CD, FCD, PA, AS, PP, Juvenile arthritis
  - Denosumab (Prolia® - Amgen) RANK-ligand inhibitor preventing osteoclast formation for osteoporosis
  - Canakinumab (Ilaris® - Novartis) anti-interleukin 1β for Muckle-Wells syndrome, familial cold auto-inflammatory syndrome and chronic infantile neurological cutaneous articular syndrome (NOMID / CINCA)
Monoclonal antibodies – PBS funded

- Rituximab (Mabthera® - Roche) for CD20+ b-cell non-Hodgkins lymphoma, CLL, RA
- Ranibizumab (Lucentis® - Novartis) for neovascular age-related wet macular degeneration
- Tocilizumab (Actemra® - Roche) for RA
- Ustekinumab (Stelara® - Janssen) for chronic plaque psoriasis
- Golimumab (Simponi® - Janssen) for RA, PA, AS
- Omalizumab (Xolair® - Novartis) for severe allergic asthma
Monoclonal antibodies not PBS funded (examples)

- Some are TGA registered (compassionate use or access programs), some under development
  - Ipilimumab (Yervoy® - BMS) for melanoma
  - Brentuximab (Adcetris® - Seattle Genetics) for Hodgkin’s lymphoma
  - Panitumumab (Vectibix® - Amgen) for colorectal cancer
  - Ofatunumab (Arzerra® - GSK) for CLL
Solanezumab

- Alzheimer’s disease
- Specifically targets β-amyloid protein
- The presence of β-amyloid plaques in the brain is thought to be diagnostic
- Currently diagnosed clinically
- No test available to confirm diagnosis
- Company has developed 2 products
  - A radio-translucent dye test
  - A monoclonal antibody to sequester β-amyloid protein
Solanezumab

- The dye compound specifically binds to β-amyloid protein in the brain
- Brain imagery therefore can determine the presence or otherwise of β-amyloid plaques
- This is diagnostic of Alzheimer’s disease
- If plaques present, administer the mab to sequester β-amyloid protein to reduce plaque formation
- Halt disease progression
- Targeted therapy
- Phase 3 trial data about to be published
- Efficacy????????
Belimumab (Benlysta®)

- Systemic lupus erythematosus (SLE)
- Complex, autoimmune, connective tissue disorder affecting multiple body systems
- Currently no specific treatment
- Symptomatic relief (NSAID’s, hydroxyurea, steroids, immunosuppressants)
- Pathophysiology is over-expression of B-lymphocyte stimulator protein (BLyS)
- Increased B-cell activity, survival and proliferation
- Over-production of auto-antibodies
Belimumab (Benlysta®)

- Belimumab is a fully human IgG1λ mab
- Specifically binds to BLyS and renders it biologically inactive
- Reduced B-cells and auto-antibodies
- First treatment specifically designed to target the underlying cause of SLE
- Indicated for patients with seropositive, moderate to severe, clinically active SLE
- Patients with active disease (SELENA-SLEDAI score ≥ 6) and autoantibody positive (anti-dsDNA titre ≥ 30iu/ml)
Monoclonal antibodies

- Several available overseas (with cost reductions)
- Significant use “off-label” of monoclonal agents for a range of immune mediated disorders
- Common in large public hospitals
- Significant financial burden
- Inpatient use
- Those that act on B-cells (eg rituximab) can treat disorders that are the result of too many, overactive or dysfunctional B-cells
  - ITP, TTP, pemphigus, glomerulonephritis, SLE, nephrotic syndrome, CLL and many more
Monoclonal antibodies

- Non-PBS funded, but provide significant clinical benefit for patients with refractory disease
- In some cases can be life saving
- Can reduce hospital admissions, LOS and reduce emergency department presentations
- Patient treated as an outpatient at home
- Therefore in some cases, use is cost effective
- Funded by the hospital and/or private insurer
Monoclonal antibodies

- The 5 largest Pharma companies in Australia
  - All have monoclonal products in their pipeline
  - Most are under clinical trial and development
  - Most in phase 2 and 3 trials
  - Most do not have a name as yet (just trial codes)
  - Expect to be released in the next 3-10 years
  - All will be expensive ($20-100K per patient per year)
  - Almost too many to keep track of
3. Receptor constructs / Fusion proteins

- Naturally occurring target receptor linked to an immunoglobulin frame
- High specificity
- Low adverse effects
- Also very expensive
- The first
  - Etanercept (Enbrel® - Wyeth now Pfizer). PBS reimbursed. Soluble tumor necrosis factor (TNF) receptor for RA, juvenile arthritis, AS, PA, PP. Approx cost $12K per annum
Fusion proteins

- Abatacept (Orenica® - BMS). Prevents full activation of T-cells. PBS reimbursed for RA
- Romiplostim (N-Plate® - Amgen). Thrombopoietin receptor agonist. PBS reimbursed for ITP

Simple proteins

- Icatibant (Firazyr® - Shire). Decapeptide for HAE as an alternative to C1-esterase. Non-PBS
Future medicines

- Unlikely to be new molecules
- Will be complex proteins and mabs
- Immune mediated therapies
- Able to treat new diseases
- In primary care
- Improvement in quality and quantity of life
- BUT..................
- Cost is a huge issue
- Who will pay?
- How can we afford these new drugs in the future?