



**Australian Government**

**Department of Defence**

**Defence Support Group**



# **The Te Genero (or Northwick Park) Incident**

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# Conducting “First-into-Man” Research

- **Relevant **Regulatory Bodies** and Documents**
  - TGA
  - NHMRC National Statement
  - AHEC
  - ICH-GCP (TGA Jul 2000)
- **Special Gene Therapy Provisions**
  - GTRAP
  - OGTR (GMAC), GTTAC, GTEC, GTCCC
- **Approvals by **Institutional Human Research Ethics Committee****
  - Requires special scrutiny
  - Expert opinion/recommendation

# Monitoring First-into-man Research

- **Differences**
  - **Informed Consent**
  - **Subject eligibility and restrictions**
  - **Study Assessments**
  - **Monitoring by Sponsor**
  - **Subjects not expected to gain therapeutic benefit**
  - **Tend to be homogeneous groups**
  - **Healthy volunteers - expectation of financial remuneration**
  - **Monitor –**
    - **first dosing day**
    - **witness key procedures – dosing and blood/tissue sampling**

# The Te Genero Incident

- **Te Genero** – a small German Biotech company formed to commercialize intellectual property from University of Wurzburg
- “Superagonistic” monoclonal antibodies - stimulate the generation of T lymphocytes (key regulators of immune response)
- In normal Immune response, Antigen Presenting Cell presents antigen and CD28 marker – co-stimulation activates T cells – and leads to the Immune Response
- Lead product TGN1412 – IgG4 superagonist with specificity for the T cell surface receptor CD28.
- Overrides both signals and leads to **activation – IMMUNE RESPONSE !**

# The Te Genero Incident (contd)

- **1<sup>st</sup> Human Trial of TGN1412 –**
  - **Dose-ranging**
  - **Cohort study**
  - **Groups of 8 subjects**
  - **Subjects dosed 10 min apart**
- **In first cohort**
  - **6/8 patients** developed serious adverse events
  - **Organ failure, respiratory distress, DIC**
  - **Transferred to ICU (part of same facility)**
  - **Initial signs appeared 50-90 min after dosing**
  - **Produced by “Cytokine Storm”/massive stimulation of Immune Response**

# The Te Genero Incident (contd)

- **Joint Enquiry Taskforce**
  - **BioIndustry Association (BIA)**
  - **Association of the British Pharmaceutical Industry (ABPI)**
- **Medicines and Healthcare products Regulatory Agency (MHRA) – Formal Enquiry**

# The Te Genero Incident (contd)

- **Joint Enquiry Taskforce**
  - Medicines that **inhibit** aspects of the immune response are widely used and **rarely have acute adverse effects**
  - Agents that **stimulate** an immune response are more **likely to lead to acute effects**
  - Decisions about first administration to man of agents that have a stimulatory effect on immune mechanisms require particularly **careful scrutiny**
  - Ensure that novel agents do not **unintentionally stimulate or activate** T cells or other immune effector cells

# The Te Genero Incident (contd)

- **Biologics** (esp. antibodies) have very high affinity and much higher species specificity for their target than classical pharmaceuticals
- Challenge in choosing a **relevant animal model** for biologics - species specificity
  - Target homology
  - Similar target expression/distribution
  - Differences in physiology and pathways
  - In vitro binding affinity
  - In vitro bioactivity or functionality
  - Biologic effects of Fc region of antibody molecule

# The Te Genero Incident (contd)

- Translation of Pre-clinical data to the Clinic
  - **Safety assessment** of a biologic - critically dependent on understanding the risks associated with intense effects upon target system and interaction with other biological systems
  - **Starting dose** must be viewed with caution; alternative dosing strategies should be considered
  - **Estimation of dose or exposure** required at bottom end of dose response curve in man is more important than level of no adverse effects (NOAEL) – termed the minimum anticipated biological effect level (MABEL)
  - **Starting dose should be below MABEL !**

# The Te Genero Incident (contd)

- **Trial Conduct**
  - **Appropriate subjects** (patients rather than healthy volunteers)
  - **Appropriate research facilities** - hospital site with intensive care facilities; emergency resuscitation team
  - Only one subject should receive active drug on first day (or at each new dose level) – **sentinel subject**
  - Appropriately **qualified investigators**
  - Exclude subjects with active or recent infections
  - Subjects requiring vaccinations should be excluded
  - No blood donations for 3 months or 5 half-lives

# The Te Genero Incident (contd)

- **Manufacturing**
  - **Great emphasis on process controls - safety, quality and efficacy**
  - **Potency assays – relevant to mechanism of action**
  - **Aggregation – biologics have this tendency**
  - **Contaminants – beware of process and product-related contaminants**
- **Protocol and Regulatory Review**
  - **Internal protocol and safety review by the research sponsor**
  - **Regulatory agency (and HRECs) must have medical staff with appropriate expertise or access to them**
  - **Sponsors must provide all appropriate information**
  - **Encourage dialogue between Regulatory Agencies and Ethics Committees**

# The Te Genero Incident (contd)

- **Medicines and Healthcare products Regulatory Agency (MHRA) – Formal Enquiry**
  - **No deficiencies in GCP**
  - **No deficiencies in GMP**
  - **No deficiencies in GLP**
  - **Problems were related to “unpredicted biological action”**
- **Problems –**
  - **First error – assume same action in humans as in animal modes (even non-human primates)**
  - **Second error – need for appropriate pharmacokinetic modeling**
  - **Third error – agonist vs antagonist modeling**
  - **Fourth error – inadequate receptor modeling**
- **Dose was 100 x greater than appropriate; product had action that was not anticipated (but should have been !)**

# The Te Genero Incident (contd)

- **MHRA Cataloged Administrative Errors –**
  - **Failure of Researchers to take full and accurate Medical History and Medical Background of all subjects**
  - **No **contract** between research sponsor and Investigators**
  - **Investigators with **inadequate training and qualifications****
  - **Two volunteers who received placebo allowed to leave facility before their safety was confirmed**
  - **Biological response in man was probably predictable (at least in part) if **literature and previous data** were properly surveyed**
  - **Study **design and methodology was flawed,****
    - **number of subjects**
    - **method of dosing**
    - **Selection of dose for humans based on animal data**

# The Te Genero Incident (contd)

- HREC Issues –
  - **Consent Form** written for Year 2 College students – too advanced for such a study
  - 29% of sentences in **Subject Information Sheet** written at graduate level
  - Principal and Senior Researchers were not directly involved in the **consent taking process**



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*Thank you for your attention*