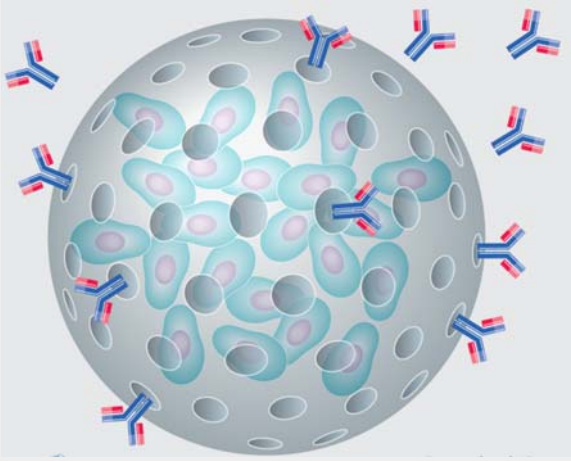
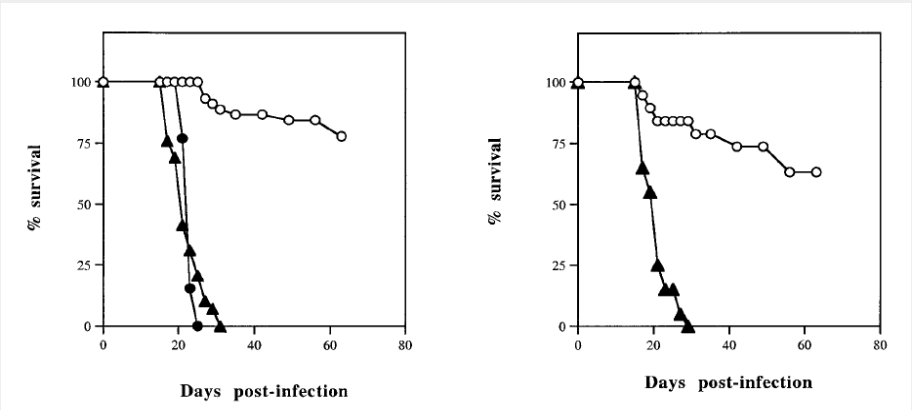


Production of Therapeutic Antibodies using Cell-in-a-Box®

One of the most important and fastest expanding areas of molecular medicine is the use of therapeutic antibodies for targeted treatment of various diseases like cancer, autoimmune disorders, inflammatory and infectious diseases. These approaches make use of the body's own immune system to eliminate cancerous cells from the body or interrupt disease mechanisms by blocking signal molecules and their receptors. Such therapies are highly specific and have great efficacy and minimal side effects. Cell-in-a-Box® technology takes immune therapy one step further and transfers the site of antibody production from the bioreactor straight into the patient's body.

To demonstrate the use of Cell-in-a-Box® technology, we have shown that encapsulated hybridoma cells can be implanted into mice where they secrete an antibody that can rescue animals from an otherwise deadly viral infection, even if the encapsulated hybridoma cells are implanted 2 days after virus infection i.e. in a therapeutic rather than vaccine/preventive scenario:



Survival of mice infected with a deadly virus after treatment with capsules producing therapeutic virus neutralising antibodies. *Left hand panel: mice were infected with a lethal dose of virus alone (▲), or with encapsulated control cells at the same time as the virus (●) or with encapsulated hybridoma cells at the same time as the virus (○). Right hand panel: mice were infected with a lethal dose of virus alone (▲), or two days after virus infection with encapsulated hybridoma cells producing the therapeutic antibody (○).*

Pelegrin et al., Immunotherapy of a viral disease by in vivo production of therapeutic monoclonal antibodies. Human Gene Therapy 11: 1407-1416.

ADVANTAGES OF *IN VIVO* MONOCLONAL ANTIBODY PRODUCTION USING Cell-in-a-Box®

Constant Antibody Production

- Avoids peaks and troughs of classical delivery resulting in:
- ✓ Better efficacy
- ✓ Lower doses required
- ✓ Less side effects / better safety profile
- ✓ Reduced chances of anti-idiotypic response
- Hybridomas or cells genetically modified to produce monoclonal antibodies can be encapsulated.

CELL IN A BOX BIOTECH

Cell-in-a-Box® can also be used to protect hybidoma cells in bioreactors acting as a protective pre-filtration device.

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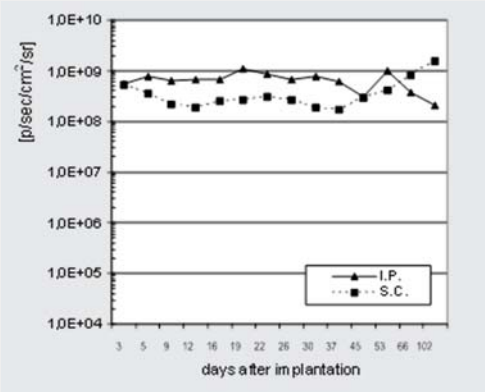
PUBLICATIONS REPORTING THE ENCAPSULATION OF HYBRIDOMA CELLS IN CELLULOSE SULPHATE

- Dangerfield et al., (2013) Chapter 3: "The diversity of uses for cellulose sulphate encapsulation". E-Book "Bioencap-sulation of Living Cells for Diverse Medical Applications", Bentham Science Publishers.
- Chua et al., (2011) A novel cell encapsulation mode for delivery of therapeutic antibodies against West Nile Virus infections that maintains steady plasma antibody levels throughout therapy**. Int J Infect Dis 14** Suppl 1, p e48
- Salmons et al., (2007) GMP production of an encapsulated cell therapy product: issues and considerations. **BioProc J 4,** 36-43
- Pelegrin et al., (2000) Immunotherapy of a viral disease by *in vivo* production of therapeutic monoclonal antibodies. **Hum Gen Ther 11**, 1407-1416
- Pelegrin et al., (1999) Encapsulated antibody-producing cells for long-term passive immunotherapy. **Pharma Tech 23**, 46-49
- Dautzenberg et al., (1999) Development of cellulose sulphate based polyelectrolyte complex microcapsules for medical applications. **Annu N Y Acad Sci 875,** 46-63
- Pelegrin et al., (1999) *In vivo* production of therapeutic antibodies by engineered cells for immunotherapy of cancer and viral diseases. **Gene Ther Mol Biol** 3, 167-177
- Pelegrin et al., (1998) Systemic long-term delivery of antibodies in immunocompetent animals using cellulose sulphate capsules containing antibody-producing cells. **Gen Ther 5**, 828-834

LONG TERM SURVIVAL OF IMPLANTED ENCAPSULATED CELLS *IN VIVO*

Encapsulated cells survive for many weeks after subcutaneous (s.c.) or intraperitoneal (i.p.) implantation in mice. Cell survival is shown here by means of live *in vivo* imaging with encapsulated cells which have been additionally modified to express luciferase.



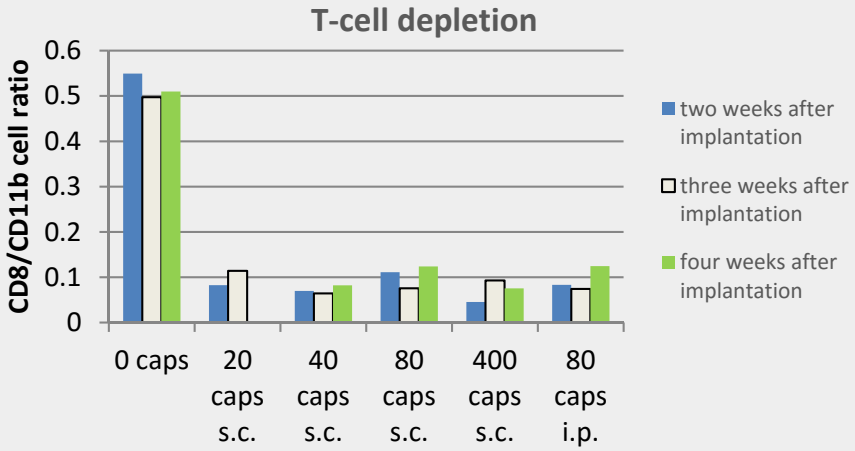
POTENTIAL APPLICATIONS OF Cell-in-a-Box® WITH ANTIBODY PRODUCING CELLS

Encapsulated antibody producing cells can be used in the clinic as well as in the establishment of new animal models.

- Continuous release of therapeutic antibodies for the treatment of:
  - Various types of cancer (breast cancer, colorectal cancer, blood cancers, head and neck cancer)
  - Autoimmune disorders (rheumatoid arthritis, multiple sclerosis, psoriasis, Crohn's disease)
  - Infectious disease
  - Cardiovascular disease
  - Transplant rejection
  - Allergy-related asthma
- To knock-out specific lineages of the immune system in animal models for research

LONG TERM DEPLETION OF SPECIFIC LINEAGES OF THE IMMUNE SYSTEM IN ANIMAL MODELS BY Cell-in-a-Box®

Cell-in-a-Box® can be used to hold and protect hybridoma cells inside the body which produce cytotoxic antibodies against certain types of immune cells. This is a very useful tool to generate animal models for the investigation of infectious and other diseases.



Cell-in-a-Box® technology was used to encapsulate hybridoma cells that produce cytotoxic antibodies against CD8+ T-cells. Different amounts of capsules were implanted into mice at different sites of the body (s.c. = subcutaneous; i.p. = intraperitoneal). Levels of CD8+ T-cells are measured and compared to CD11b+ cells which are not affected by the treatment. ***The results show that long-term depletion can be achieved form a single implantation of capsules.***

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