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The Therapeutic Potential of Cell Encapsulation Technology for Drug Delivery in Neurological Disorders

Carlos Spuch and Carmen Navarro
University Hospital of Vigo, Department of Pathology and Neuropathology, Vigo, Spain

1. Introduction

The brain can be damaged by a wide range of conditions including infections, hypoxia, poisoning, stroke, chronic degenerative disease and acute trauma. Some of the most problematic forms of brain damage are those associated with chronic neurodegenerative diseases or acute brain trauma as a result of contusive or penetrating injury. In these cases, damage results in the loss of specific populations of neurons and the development of defined psychiatric or neurological symptoms. Current treatments for these problems are designed to pharmacologically modify disease symptoms; however, no therapies are yet available that fully restores lost function or slow ongoing neurodegeneration in the brain. Many promising therapies with growth factors has been implicated in brain regeneration, repair and neuroprotection in the central nervous system produced interesting results, such as vascular endothelial growth factor (VEGF) (Spuch et al. 2010) brain derived growth factor (BDNF) (Malik et al., 2010) or nerve growth factor (NGF) (Sharma. 2010). However, the critical problem is the way to deliver, in a continuous and localized manner, and more important is to supply physiological amounts of growth factors into focus damage of the brain tissue. One interesting approach is cell encapsulation, in which engineered somatic cells are protected against immune cell mediated and antibody-mediated rejection through immobilization in a polymer matrix surrounded by a semipermeable membrane. The latter regulates the bidirectional diffusion of nutrients, allowing the controlled and continuous delivery of therapeutic proteins in the absent of immunosupression in the proper concentration and localization.

Encapsulated cells offer enormous potential for the treatment of human disease. Many attempts have been made to prevent the rejection of transplanted cells by the immune system. Cell encapsulation is promising machinery for cell transplantation and new materials and approaches were developed to encapsulate various types of cells to treat a wide range of diseases.

Cell microencapsulation holds promise for the treatment of many diseases by the continuous delivery of therapeutic products. The complexity of many neurological diseases needs the developing of new drugs and especially new pathways to deliver the drug at proper concentration and into the correct localization. One critical problem is the way to deliver, in a continuous and localized manner, physiological amounts of drugs. One

promising technology is the developing of new biomaterial components with the capacity of envelope drugs, cells or tissues, being able to distribute the drug therapy, and, at the same time, to be isolated of immune system. The main goal of microcapsules technology is the capacity to release growth factors, peptides, proteins or hormones in a precise location and to keep isolated from immune system attack. This is the critical issue for the long-term efficacy of this biotechnology, due the core of microcapsules is made of cells or tissue that are able to regulate, by themselves, the release of the necessary drug at the implanted tissue, and at the same time, the grafts are isolated from the immune system.

The objective of this chapter is to summarize the recent investigations and news related with cell microencapsulation technology, and the possible therapeutic applications of growth factors-secreting cells on brain impairment in different neurological disorders and brain tumours. We will comment our investigations related last publications and patents in cell microencapsulation and our findings confirming the evidence of a potential therapeutic benefit of growth factors therapy in neuroprotection with VEGF and the last results with BDNF microcapsules implants such as therapeutic value in the treatment and prevention of brain damage.

2. Overview

Each year over 10 million people globally suffer from neurodegenerative diseases. This figure is expected to grow by 20% over the next decade as the aging population increases and lives longer. It is the fourth biggest killer in the developed world after heart, cancer and stroke. There are millions of sufferers worldwide, and can occur at any age but it is more common among the elderly. Many similarities appear which relate these diseases to one another on a sub-cellular level. Discovering these similarities offers hope for therapeutic advances that could ameliorate many diseases simultaneously. Gene defects play a major role in the pathogenesis of degenerative disorders of the nervous system; however a feature observed in the most common neurodegenerative disorders is the dichotomy between familial forms and seemingly non-familial or sporadic forms characterized by the persistent and progressive loss of neuronal subtypes.

The most common neurodegenerative diseases are Alzheimer disease, Parkinson disease, Lewy body dementia, frontotemporal dementia, amyotrophic lateral sclerosis, Huntington disease, and prion diseases. The most widely recognized are Alzheimer's disease and Parkinson's disease, which are among the principal debilitating conditions of the current century. Approximately 24 million people worldwide suffer from dementia, of which 60% is due to Alzheimer's disease occurs in 1% of individuals aged 50 to 70 years old and dramatically increases to 50% of those over 70 years old [Ferri et al, 2005). Alzheimer's disease is typified clinically by learning and memory impairment and pathologically by gross cerebral atrophy, indicative of neuronal loss, with numerous extracellular neuritic amyloid plaques and intracellular neurofibrillary tangles found predominantly in the frontal and temporal lobes, including the hippocampus (Morgan, 2011). The number of cases of dementia was studied by European Community Concerted Action on the Epidemiology and Prevention of Dementia group (EURODEM). The total cost of illness of dementia in the European Union27 in 2008 was estimated to be EUR 160 billions, EUR 22.000 per person with dementia per year. This study also estimated in the United Kingdom that 683.597 people suffered from dementia in 2005, with the total forecasted to increase to 940.110 by 2021 and 1.735.087 by 2051. The economists of United Kingdom calculate in £ billion in care

costs and lost of productivity. This terrible estimation will be similar in the rest of European countries (Brayne et al, 2011 and Virues-Ortega, 2011). Only in United States Alzheimer's disease is the sixth leading cause of all death and is the fifth leading cause of death in Americans aged with more than 65 years-old. (Alzheimer's association, 2011). Although other major causes of death have been decrease, deaths because of dementia have been rising dramatically, and the worst is that the true social impact is incalculable.

Few cases of dementia are diagnosed in early stages, as many of the associated symptoms, e.g. memory loss, could be attributed to other conditions such as depression, diabetes, thyroid abnormalities, delirium, alcoholism or simple ageing. This makes diagnosis particularly difficult, such that it may take up to one year or longer for a final diagnosis to be made. Formal testing for dementia requires mental ability tests, such as the Mini Mental State Examination (MMSE), a review of medical history and current medications, an examination of biological markers such as levels of abnormal proteins associated with different dementias, and sometimes imaging scans such as magnetic resonance imaging (MRI) scan to detect changes in the brain. Current treatment options for dementias leave much to be desired. Existing medications, which either prevent the breakdown of neurotransmitters or modulate key receptors in the brain, can temporarily ease some of the cognitive decline associated with the disease, but they do nothing to halt or reverse its progression. And although scientists are developing new therapeutics that target the cause of the different dementias more directly, even these latest experimental drugs might do little to help patients. To make headway, some neuroscientists and neurologist experts now argue that the research community must fundamentally change how it diagnoses the disease and designs clinical trials.

There is still no cost-effective method of identifying people with dementia through population screening. Early diagnosis of dementia is important, allowing those with dementia and their carers to plan better for their future and to start treatments that may slow disease symptoms. Nowadays, pharmaceutical agents that are used to treat brain disorders are usually administered orally, such as donepezil, memantine, rivastigmine, galantamine and tacrine for Alzheimer's disease (Pasic et al, 2011); or levodopa, entacapone, pramipexole and ropinerole for Parkinson´s disease (Morley & Hurtig, 2010). However, most of the ingested drugs does not target the brain in full conditions and is, instead, metabolized totally or partially by the liver. This inefficient utilization of drug may require ingestions of higher drug concentrations that can produce toxic effects such as cardiotoxicity, hepatotoxicity and nephrotoxicity. Also, many therapeutic agents are poorly soluble or insoluble in aqueous solutions. These drugs provide challenges to delivering them orally or parentally, however these compounds can have significant benefits when formulated through nanoparticles or microcapsules technology. More efficient use of the drug can be realized both by eliminating liver metabolism and directly targeting the brain.

Notwithstanding these difficulties, the nanotechnology may provide a solution to overcome the diagnostic and neurotherapeutic challenges for neurodegenerative and neurological diseases. Nanotechnology employs engineered materials or devices with the smallest functional organization on the nanometre scale (1–100 nm) that are able to interact with biological systems at the molecular level. Nanoparticles are able to penetrate the blood brain barrier of *in vitro* and *in vivo* models. Nanotechnology can therefore be used to develop diagnostic tools as well as nano-enabled delivery systems that can bypass the blood brain barrier in order to facilitate conventional and novel neurotherapeutic interventions such as drug therapy, gene therapy, and tissue regeneration. Nanotechnology is currently being

used to refine the discovery of biomarkers, molecular diagnostics, drug discovery, and drug delivery, which could be applicable to the management of serious neurodegenerative diseases such as Alzheimer's disease or Parkinson's disease.

The other great promise in the treatment of neurodegenerative diseases is the microencapsulation of cell types secreting bioactive substances locally in the damage area of the brain. The main handicap for the delivery of potentially therapeutic drugs to the brain is hindered by the different blood brain barriers, which restricts the diffusion of drugs from the vasculature to the brain parenchyma. One means of overcoming the blood brain barrier is with cellular implants that produce and deliver therapeutic molecules. Polymer encapsulation, or immunoisolation, provides a means of overcoming the blood brain barrier to deliver therapeutic molecules directly into the central nervous system region of interest. Immunoisolation is based on the observation that xenogeneic cells can be protected from host rejection by encapsulating, or surrounding, them within an immunoisolatory, semi permeable membrane. Cells can be enclosed within a selective, semi permeable membrane barrier that admits oxygen and required nutrients and releases bioactive cell secretions, but restricts passage of larger cytotoxic agents from the host immune defence system. The selective membrane eliminates the need for chronic immunosuppression of the host and allows the implanted cells to be obtained from nonhuman sources.

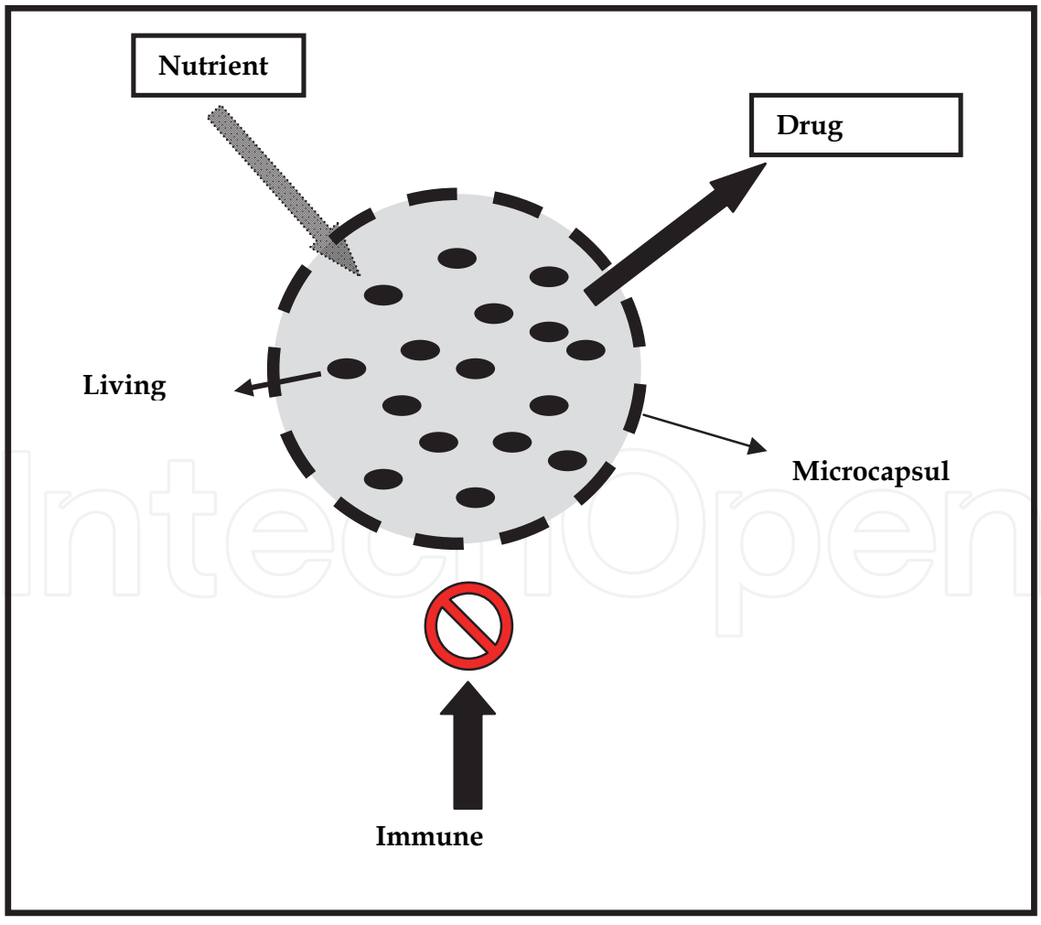

Fig. 1. Scheme of microcapsules containing living cells.

Likewise, a detailed understanding of their genetic and molecular basis will be essential for the development of effective strategies aimed at the early prediction and early prevention/treatment of these devastating diseases. In this review, microencapsulation technology for treating CNS diseases is updated from considerations of device configurations, membrane manufacturing and characterization in different preclinical models of neurodegenerative diseases.

3. Nanotechnology

The most promising aspect of pharmaceuticals and medicine as it relates to nanotechnology is currently drug delivery. Nanotechnology will play a key role developing new diagnostic and therapeutic tools. Nanotechnologies use engineered materials with the smallest functional organization on the nanometre scale in at least one dimension. Some aspects of the material can be manipulated resulting in new functional properties.

Nanoparticles hold tremendous potential as an effective drug delivery system. In this chapter we discuss recent developments in nanotechnology and especially in microencapsulation cell technology for drug delivery, image diagnostics and new therapeutic treatments. To overcome the problems of gene and drug delivery, nanotechnology has gained interest in recent years. Nanosystems with different compositions and biological properties have been extensively investigated for drug and gene delivery applications. To achieve efficient drug delivery it is important to understand the interactions of nanomaterials with the biological environment, targeting cell-surface receptors, drug release, multiple drug administration, stability of therapeutic agents and molecular mechanisms of cell signalling involved in pathobiology of the disease under consideration. Several anti-cancer drugs including paclitaxel, doxorubicin, 5-fluorouracil and dexamethasone have been successfully formulated using nanomaterials. Quantom dots, chitosan, Polylactic/glycolic acid (PLGA) and PLGA-based nanoparticles have also been used for *in vitro* RNAi delivery. Brain cancer, neurological and neurodegenerative diseases are one of the most difficult diseases to detect and treat, mainly because of the difficulty in getting imaging and therapeutic agents past the blood-brain barrier and into the brain. Anti-cancer drugs such as loperamide and doxorubicin bound to nanomaterials have been shown to cross the intact blood-brain barrier and released at therapeutic concentrations in the brain.

4. Process of microencapsulation

The process of microencapsulation has been used for many years, with the introduction of many diverse applications of the basic principle. Microencapsulation is a process by which very tiny droplets or particles of liquid or solid material are surrounded or coated with a continuous film of polymeric material. Most microcapsules have diameters between a few micrometers and a few millimetres. The idea was based on natural subcellular organelles which contain proteins, growth factors or enzymes. The first suggestion was made in 1964 about that encapsulation could be used to replace cells or cell products lost due to genetic defects (Chang, 1964). Although, microencapsulation as a viable procedure to immunoisolate cells for transplantation was introduced more than twenty years ago (Lim & Sum, 1980), it has had a slow progress towards clinical application. Microencapsulation technology holds promise methodology for the treatment of many diseases by the

continuous delivery of therapeutic products, for example, due to slow production rates and the appearance of fibrotic overgrowths around the capsules, which can result in endotoxin contamination, e.g., oxygen and nutrient deprivation of the enclosed cells. However, when we talk about how to apply this promising technology in the treatment of neurological and a neurodegenerative disease presents a major problem, how to introduce this therapeutic agent into the brain in a safe an undamaged manner.

The biocompatibility of the microcapsules and their biomaterials components are a critical issue for the long-term efficacy of this technology. Microcapsules are polymers that can carry multiple therapeutic agents such as cells, drugs or proteins. The method of producing and designing these polymers is one of the most important steps in the developing of microencapsulated pharmaceutical products. Polymers are usually formulated using hydrophobic synthetic polymers and copolymers such as PLA and PLGA, polyacrylates and polycaprolactones or natural polymers such as albumin, gelatine, alginate, collagen and chitosan (Orive et al, 2003a). PLA and PGLA are the biomaterials most investigated for microencapsulation for drug delivery (Jain, 2000 and Langer, 1997). The alginate composition and purification, the selection of the polycation, the interactions between the alginates and the polycation, the microcapsule fabrication process, the uniformity of the devices and the implantation procedure are key factors for the correct developing of biocompatible microcapsules.

Microcapsules comprise a wall which surrounds an encapsulated material. Microencapsulation includes bioencapsulation which is more restricted to the entrapment of a biologically active substance generally to improve its performance or enhance its shelf life. Chemical and physical methods for cell immobilization are fairly diverse, and a large number of systems have been created that entrap catalytically active cells in various matrices, such as carrageenan, alginate, polyacrylamide and polyethylene glycol gels, as well as polyurethane foams (Orive et al, 2009). A novel polymeric methodology for microencapsulation based on immobilized living cells has been developed and now is available for different applications. This methodology is based on the formation of gel structures during the process of cooling and subsequent freezing of cell suspensions in polymer solutions.

The wall of the microcapsules should protect the material from external environment and is mainly made by polymers. The polymer used in the encapsulation art has to be biocompatible and biodegradable polymer (Mulqueen et al, 2010). The molecular weight of a polymer is important because influences the biodegradation rate although any desired molecular weight can be used, depending of the properties for the microparticles desired. In certain aspects a high strength polymer is need it to meet strength requirements, or low molecular weight polymers when resorption time is priority. For a diffusional mechanism of bioactive agent release, the polymer should remain intact until all of the drug is released from the polymer and then degrade. In some aspects, the time interval to degrade the polymer within a wanted time can be from about less than one day to months or years. Also, the selection of the polymer can influence the desired lapse time after the implantation. For example, a recent patent disclose a microencapsulation process using epoxy resin is able to change this properties (Cen et al, 2010). An improvement in this process of generation of new polymers was described by a new patent, where new emulsions and solvents it was generated better walls for the microcapsules (Raiche et al, 2010).

After designing the right biodegradable polymers, microencapsulation has permitted controlled release delivery systems. These revolutionary systems allow controlling the rate, duration and distribution of the active drug. With these systems, microparticles sensitive to the biological environment are designed to deliver an active drug in a site-specific way. One of the main advantages of such systems is to protect sensitive drug from drastic environment and to reduce the number of drug administrations for patient (Spuch & Navarro, 2010).

5. Cell microencapsulation implants to treat brain diseases

Drugs agents that are used to treat central nervous system are usually administered orally. However, the penetration of drug into brain decrease exponentially with the distance from cerebrospinal fluid surface, it is necessary to administer high concentrations of drug into cerebrospinal fluid compartment. The ependymal surface is exposed to very high drug concentration, which can have toxic side effects. The treatments with growth factors are very promising; however there are side effects due to the route of administration. It was demonstrated the beneficial effects of different growth factors for the treatment of various brain diseases. For example, it was published the beneficial effects of IGF-I (insulin growth factor-I) associated to a significant increase in brain amyloid-beta complexed to protein carriers such as albumin, apolipoprotein J or transthyrretin, supporting a therapeutic use of IGF-I in neurodegenerative diseases (Carro et al, 2006a, 2006b). Moreover, it was showed the intracerebroventricular (icv) administration of NGF (nerve growth factor) resulted in axonal sprouting and Schwann cell hyperplasia on the ependymal or arachnoids surface (Day-Lollini et al, 1997). The icv administration of fibroblast growth factor (FGF)-2 results in periventricular astrogliosis (Yamada et al, 1991). Also, the icv administration of glial-derived neurotrophic factor (GDNF) in Parkinson's disease, resulted in no penetration of the GDNF into substance nigra or into the caudate putamen nucleus, but did result in high incidence of adverse events (Nutt et al, 2003). Conversely, it is sometime desirable to deliver high concentrations of drug to the meningeal surface of the brain, such as in the treatment of meningeal infiltration of leukemia cells, and this can be achieved with intrathecal drug administration through microcapsules implants.

However, most of these drugs does not target the brain because does not across the blood brain barrier. This inefficient utilization of drug can produce toxic effects in other organs. More efficient use of the drug can be realized both by elimination liver metabolism and directly targeting the brain. Based on these premises, the promising features of microencapsulation technology belong to the direct administration of microencapsulated drug into the brain (Dou et al, 2006).

The microcapsules to be an implantable drug delivery device has to contain a carrier fluid the will dissolve the drug when freed from the capsule, a drug releaser for freeing the microencapsulated drug from the capsule, a reservoir in which the carrier fluid dissolve the drug. An example of the first problems in the microencapsulation technology was the therapeutic use of NGF in the prevention and treatment of many neurodegenerative diseases, such as Alzheimer's disease, degeneration of cholinergic neurons or the natural effects of aging in the brain. The first evidences showed that icv administration of NGF directly or with osmotic pumps prevented the degeneration of these neurons (Cleland et al 2007); however NGF infusion into the brain may be complicated due to stability and degradation in some implants (Schecterson & Bothwell, 2010). The first improvements were

made with the NGF microencapsulation, increasing the stability and controlling the release of recombinant NGF, however this type of microcapsules was not enough.
There are various potential micro-implants employed for the treatment of neurological and neurodegenerative disorders, such as polymeric nanoparticles, microcapsules, hydrogels, or liposomes.

5.1 Nanoparticles

The advent of nanotechnology can provide a solution to overcome the future diagnostic and new neurotherapeutic challenges for neurodegenerative diseases as Alzheimer's disease and Parkinson's disease. This technology employs engineered materials with the smallest functional organization on the nanometre scale that are able to interact with biological systems at the molecular level. Nanoparticles are able to penetrate the blood brain barrier of *in vitro* and *in vivo* models disrupting the temporally the barrier and allowing the incorporation the therapeutic agents into the brain (Rempe et al, 2011). One interesting pathway to reach introduce drugs with nanoparticles into the brain can be with previous phagocytise using immune cells that are able to across the blood brain barrier. For example, there is an invention where involves delivering a drug by using macrophages present in the patient's cerebrospinal fluid that are capable to reaching the brain transporting the drug. This particular mode of delivery utilizing macrophages needs of previous uptake by the macrophages of nanoparticles loaded with the drug. The great advantage of this methodology is that these cells are not limited to macrophages, it is possible the use of monocytes, granulocytes, neutrophils, basophils and eosinophils.
Major future and promising uses of nanoparticles can therefore be to develop diagnostic tools. For example, amyloid plaques are one of the pathological hallmarks of Alzheimer's disease, the visualization of amyloid plaques in the brain is important to monitor the progression of this disease and to evaluate the efficacy of therapeutic interventions. Recently, many groups are developing new contrast agents to detect amyloid plaques *in vivo* using ultrasmall superparamagnetic iron oxide nanoparticles, chemically coupled with amyloid-beta (1-42) peptide to detect amyloid deposition (Yang et al, 2011). Further, nanoparticles are currently being used to refine the discovery of biomarkers and molecular diagnostics, which could be applicable to the management of neurodegenerative and neurological diseases (Sahni et al, 2010). Current pharmacotherapies for neurodegenerative diseases that have been successfully encapsulated in nanoparticles are polyphenolic compounds, (EGCG, apolipoprotein E containing curcumin or resveratrol), hormones (estradiol, melatonin, vasoactive intestinal peptide) and amyloid targeted drugs (thioflavin-T and S, coenzyme Q10, amyloid or gold).

5.2 Microcapsules

The technology of cell microencapsulation represents a strategy in which cells that secrete therapeutic products are immobilized and immunoprotected within polymeric and biocompatible devices (Orive et al, 2003b). One of the main advantages of cell microencapsulation is for the treatment of neurological disorders, where some drugs have potential therapeutic possibilities, such as growth factors or peptides, however only at low and constant concentrations. These microcapsules implants are able to secrete only the drug required by the damaged tissue, because the implants with microencapsulated cell are formed by live cells. These immobilized live cells that over-express the drug are able to

regulate themselves for the endeavour. One potential impact of this drug delivery approach is that administration of immunosuppressants and implementation of strict immunosuppressive protocols can be reduced or eliminated, therefore the serious risks associated with these drugs can also be avoided.

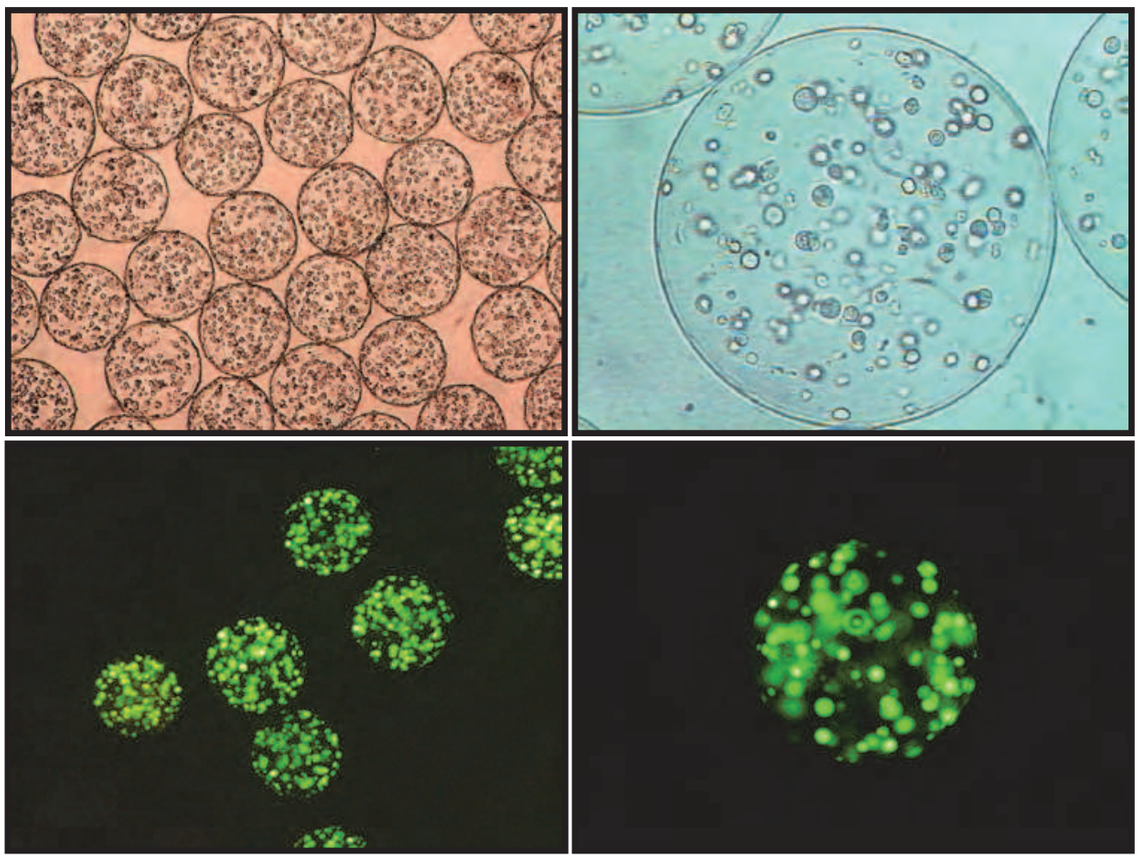

Fig. 2. Light microscopy (upper) and fluorescence microscopy (bottom) of encapsulated cells.

Based on this concept, a wide spectrum of cells and tissues may be immobilized, enhancing the potential applicability of this strategy to the treatment of numerous diseases. The therapeutic use of immortalized lines appropriately modified is employed as a medicinal product in different microcapsules for future treatments in brain disease. Last year, our group has patented one methodology to treat neurodegenerative diseases based in the cell microencapsulation of VEGF (vascular endothelial growth factor) overexpression cells. One goal of theses findings was to develop the therapeutic methodology without alter the blood brain barrier and to reduce the damage of the brain increasing the vascularity at cortical levels and reducing the amyloid-beta deposits (Spuch et al, 2010). Other example using encapsulation procedures are the case of microencapsulation of PC12 cells (dopaminergic cell line) and also embryonic grafts of dopaminergic cells were able to ameliorate behaviours in rat and primates after the implants these microcapsules in experimental parkinsonian models (Cherksey et al, 1996). Recently, based on a previous patent for the treatment of brain tumours with microcapsules, it was published a promising therapy against

Alzheimer's disease with the local and long term administration of CNTF (ciliary neurotrophic factor) using recombinant cells encapsulated with alginate secreting this neurotrophin factor (Orive et al, 2010 & Keunen et al, 2011).

In recent years microencapsulation technology and gene therapy was combined to be use as new therapy to deliver specific substances to target cell in brain tumours. The treatment of brain tumours represents one of the most challenges in oncology. Many anti-cancer drugs developed the last years did not provide effects in brain tumours due to impossibility of cross the blood brain barrier. In particular, the developing of microcapsules loaded with anti-cancer drug implanted into brain allows the treatment of tumours directly in the origin of target cells. Some years ago, it was patented a new system for therapy of malignant brain tumours (Keunen et al, 2011). This methodology used alginate-encapsulated H528 cells releasing antibodies stabilized potentially inhibit a heterogeneous glioma cell population. These microcapsules were implanted into brain and after slow and controlled distribution within all cerebrospinal fluid compartments of the antibodies during 9 weeks, the glioma were significantly reduced. This example can be apply for other potential anti-cancer drugs combined with different producer cells increasing the specificity of the treatment and the potential delivery system for specific brain tumours (Thorsen et al, 2000). Further, new biomaterials are playing an increasingly important role in developing more effective brain tumour treatments. This new biomaterials can also serve as targeted delivery devices for novel therapies including gene therapy, photodynamic therapy, anti-angiogenic and thermotherapy playing key roles in the diagnosis and imaging of brain tumours by revolutionizing both preoperative and intraoperative brain tumour detection.

Monoclonal antibodies have been envisioned as useful agents for human therapeutic and diagnostic applications *in vivo*. Recent results from human clinical trials suggest that this potential is becoming a reality. Attention is now shifting to the development of methods to produce monoclonal antibodies of a quality acceptable for widespread human use and in sufficient quantity to be a commercially viable product. Microencapsulation technology has been demonstrated to be suited to the large-scale production of both human and murine monoclonal antibodies of high purity and activity, for use in applications *in vivo*. It was previously comment the possibility of encapsulate antibodies for the treatment of brain tumours. The same technology using anti-VE-cadherin monoclonal antibodies allowed open a new alternative for the inhibition of angiogenesis and demonstrates the feasibility of using microencapsulated cells as a control-drug delivery system (Orive et al, 2001). Also, it was recently patented the use of human IgM antibodies encapsulated in alginate with demonstrated activity in the treatment of demyelinating diseases as well as other diseases of the central nervous system that are of viral, bacterial or idiopathic origin, including neural dysfunction caused by spinal cord injury (Rodriguez et al, 2009).

Currently, there is ongoing several clinical trial where it is implicated the microencapsulation technology. There is an interesting clinical trial to treat Parkinson's disease with the product named Spheramine. This product, developed by Titan Pharmaceuticals, is currently under safety and efficacy study. This product consists on cultured human retinal pigment epithelial cells on microcarriers. These microcarriers are implanted stereotaxically into both hemispheres of Parkinson's disease patients, and will be evaluated during 24 months (NCT00206687 & NCT00761436). Another two clinical trials are the work from Neurotech Pharmaceuticals to look at the safety and effectiveness of CNTF

implants on vision in participants with atrophic macular degeneration (NCT00447954) and retinitis pigmentosa (NCT00447980). The implant is a small capsule that contains human retinal pigment epithelium cells. These cells have been given the ability to make CNTF and release it through the capsule membrane into the surrounding fluid.

5.3 Hydrogels

The microencapsulation technique might to solve different problems with the implantation in several tissues. The brain sometime does not allow the implantation of structures into the brain because there is not enough space. However, one solution to this problem can be the use of hydrogels. In this case, cell clusters are immobilized in hydrogel microspheres. Typically, the semipermeable membranes formed at the microsphere surface, the most common chemical system of the capsule membrane is by ionic or hydrogen bonds between two weak polylectrolytes such as acidic polysaccharides (alginic acid) and cationic polysaccharides (poly-lysine) (Bronich et al, 2006 & Bontha et al, 2006). The entrapment of the cells is obtained by the gelation. These types of microcapsules were developing for new therapies to treat diabetes. However, this technology is more promising for neurological and neurodegenerative diseases. Recently, it was published that the administration of VEGF as a potential neuroprotective strategy following cerebral stroke (Emerich et al, 2010) or Alzheimer's disease (Spuch et al, 2010). VEGF has a short half time life and limited access to the brain parenchyma following systemic administration. Previously, we commented the administration of VEGF in cell microcapsules implants, now we describes the incorporation of VEGF into a sustained release hydrogel delivery system located directly to the site of infarction.

5.4 Liposomes

Liposomes are vesicular structures composed of uni- or multi-lamellar lipid bilayer surrounding internal aqueous compartments. The main advantage of these structures is the relatively large quantities of drug can be incorporated into compartment. However, liposomes structures present various problems related to administration pathway. Orally administration is difficult related to the low pH of the stomach and the presence of bile salts tends to destabilize the liposome complex. Also, liposomes are highly susceptible to destruction via uptake by reticulo-endothelial system of the macrophages. A way of protecting liposomes was studied increasing stable bilayers and regulating the release profile of the liposome.

Between all the applications of this technology, the developing of suitable liposomal carrier to encapsulate neuroactive compounds is very promising. These liposomes are stable enough to carry them to the brain across the blood brain barrier with the appropriate surface characteristics for an effective targeting and for an active membrane transport. It was described the formulation of liposomes with monosialoganglioside allowing the brain uptake of these liposomes and of course making then good candidates as drug delivery system to the brain (Mora et al, 2002).

A novel liposome delivery system was developed for directed transport into olfactory epithelium cells with polyethylene glycol (PEG)ylated (stealth) immunoliposomes directed against human gliofibrillary acidic protein (GFAP). The handicap of theses liposomes are being incapable of penetrating the unimpaired blood brain barrier, nevertheless, may be

useful in delivering drugs to glial brain tumours (which continue to express GFAP) or to other pathological loci in the brain with a partially disintegrated blood brain barrier (Chekhonin et al, 2005 & Chekhonin et al, 2008). Furthermore, this transport system mediating liposomes holds promise for the delivery of bioactive substances to olfactory epithelial cells and modulation of their capacity to stimulate axonal regeneration.
Microencapsulation technology has proven to have great potential for providing neuro-therapeutic modalities to limit and reverse the neuropathology of neurodegenerative diseases. Based on this concept our group is working in the establishment of new synapses in the peripheral and central nervous system activating the long-distance retrograde neurotrophin signalling. It is well known that target derived NGF is necessary and sufficient for formation of post-synaptic specialization on dendrites of sympathetic neurons. Based on this concept, we are working with microencapsulation technology to releases NGF with implants outside of brain and induce the formation of new synapses in brain region damaged by ictus and neurodegenerative diseases.

5.5 Exosomes

Recently it has developed a new method for delivering complex drugs directly to the brain. This new way to get effective drugs from blood to the brain it is the possibility to overcome the obstacle utilizing exosomes. New studies demonstrated that exosomes are tiny particles produced naturally by the body and the last investigations adapted them to deliver a gene therapy.
Exosomes are small capsules that are produced by most cells in the body in varying amounts. These natural nanoparticles are thought to be one of the ways cells communicate with each other and the body's immune system. When exosomes break off from the outer walls of cells, they can take various cellular signals and genetic material with them, transporting this material between different cells. The exosomes, injected into the blood, are able to ferry a drug across the normally impermeable blood-brain barrier to the brain where it is needed. Lately, it was published that exosomes endogenous vesicles that transport RNAs and proteins can deliver short interfering RNA to the brain mice. The therapeutic potential of exosome mediated short interfering RNA delivery was demonstrated by the strong messenger RNA and protein knockdown of BACE1, a therapeutic target in Alzheimer's disease, in wild-type mice (Alvarez-Erviti et al, 2011).
Also, it was report that exosomes can deliver anti-inflammatory agents, such as curcumin, to activated myeloid cells in vivo to treat inflammation-related autoimmune/inflammatory diseases and cancers. The specificity of using exosomes as a drug carrier creates opportunities for treatments of many inflammation-related diseases without significant side effects due to innocent bystander or off-target effects (Sun et al, 2010).

6. Conclusions

The natural barrier exists to protect the brain, preventing bacteria from crossing over from the blood, while letting oxygen through. However, this has also produced problems for medicine, as drugs can also be blocked. Currently, less than 5% of drugs are able to cross the barrier; one example is temozolomide, which is the only chemotherapy available for treating brain tumours such as glioblastoma multiforme and progressive anaplastic astrocytoma. These tumours have a poor prognosis and continue to grow, even after

treatment with temozolomide. Notwithstanding these difficulties, we expect that cell microencapsulation technology will have a key role in the systemic application of new drugs, such as, growth factors, peptides or hormones. Recent advances in the field have provided novel drugs to fight against neurological or metabolic disorders. Nowadays is impossible to treat correctly many diseases mainly for the localization of damaged tissue or the complexity of tissue affected. The complexity of the disease, and many times, the localization of the tissue damage, difficult the possible treatment, for example, the brain are isolated by the blood brain barrier. Likewise, it is very important a detailed understanding of their genetic basis. Future genetic and cellular studies will be essential for the development of effective strategies aimed at the early prediction and early prevention/treatment of these devastating diseases. Therefore, new therapies for these hard to treat brain diseases are needed urgently alongside brain malfunctions such as Alzheimer's, Parkinson's and more.

Nanoparticles technology is currently being used to refine the discovery of biomarkers, molecular diagnostics, drug discovery, and cell microencapsulation technology for drug delivery, which could be applicable to the management of neurodegenerative diseases. It well demonstrated that the application of neurotrophic factors is able to modulate neuronal survival and synaptic connectivity and it is a promising therapeutic approach for many neurodegenerative diseases. However, it is very difficult to ensure long-term administration into the brain, this technology allow us to use recombinant cells secreting different neurotrophic factors encapsulated in alginate polymers. The implantation of these bioreactors in the damage region of the brain is another handicap to be solved; the correct implantation is associated with the robust improvement of cognitive performances.

One of the most important handicaps for the clinical application of cell microencapsulation technology may represent an improvement of the monitoring and biosafety of encapsulated cells. A significant breakthrough to overcome these problems associated with cell therapy was solved recently by Pedraz's group. They are developing a promising method where demonstrated the simultaneous monitoring and pharmacological control of myoblasts-containing alginate microcapsules. They introduced in the cells the SFG(NES)TGL triple reporter retroviral vector, which contains green fluorescence protein (GFP), firefly luciferase and herpes simplex virus type 1 thymidine-kinase (HSV1-TK). With this reporter they are able to follow up by luminometry if the cell is alive. Also, the treatment with the thymidine-kinase substrate ganciclovir caused death of microencapsulated myoblasts. Hence, they conclude that incorporation of the SFG(NES)TGL vector into microencapsulated cells represents an accurate tool for controlling cell location and viability in a non-invasive way. Moreover, cell death can be induced by administration of ganciclovir, in case therapy needs to be interrupted. This system may represent a step forward in the control and biosafety of cell- and gene-therapy-based microencapsulation protocols (Catena et al, 2010).

The development of novel therapeutic strategies for neurodegenerative and neurological diseases represents one of the biggest unmet medical needs today. The rapid developing of cell microencapsulation technology may provide a solution to overcome these diagnostic and neurotherapeutic challenges for neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease. Although this is a significant and promising result, there are a number of steps to be taken before this new form of drug delivery can be tested in

humans in the clinic. Nanotechnology can therefore be used to develop diagnostic tools as well as enabled delivery systems that can bypass the blood brain barrier in order to facilitate conventional and novel neurotherapeutic interventions such as drug therapy, gene therapy, and tissue regeneration.

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