# Bioprocess miniaturization: Development and optimisation

*Tuesday 26th November 2013*
Cineworld: The O2, London, SE10 0DX, UK

Miniaturisation and automation of bioprocess development continues to be a rapidly expanding area of interest since the technologies promise to reduce biopharmaceutical development time and cost. This meeting will focus on recent technologies used in high throughput bioprocess development, from clone selection through to analysis of final product and formulation. Expert speakers will describe the development and use of current miniaturisation technologies together with the technical and regulatory hurdles that must be overcome to facilitate wider industrial uptake.

This event has CPD accreditation and is part of **The 2013 BioProcessing Summit** - www.BioprocessingSummit2013.com

**Meeting chair:** *Professor. Chris Lowe*, Department of Chemical Engineering and Biotechnology, University of Cambridge, UK

**Who Should Attend:**
Biotech and Pharma Industry: CEOs, Chief Scientists, Group Heads, Senior and Junior Scientists, Research Managers
Academic and Research Institutes: Group and Lab Heads, Postdoctoral Scientists and Research Students

The deadline for abstract submissions for oral and poster presentation has now passed.

Talk times include 5 – 10 minutes for questions

9:00 – 9:45 **Registration**

9:45 – 10:00 **Introduction by the Chair**: *Professor. Chris Lowe*, Department of Chemical Engineering and Biotechnology, University of Cambridge, UK

10:00 – 10:30 **Confinement phenomenon based bio-process intensification using monolithic microreactors**
*Professor Galip Akay*, School of Chemical Engineering and Advanced Materials, Newcastle University, UK
Bio-Process intensification, B-PI (by a factor of 5-200 fold compared with batch processing) is achievable using monolithic microreactors with well defined physical and biochemical structure of pores used as support for bacteria or cells. This enhancement is due to 'confinement phenomenon' in which the behaviour of microorganisms is dependent on their confining environment. Recent examples of B-PI pioneered at Newcastle University include fermentation, antibiotics and enzyme production as well as tissue engineering and Agri-Process Intensification through bacterial nitrogen fixation by plants. Mechanism of B-PI will be discussed.

10:30 – 11:00 **Microfluidic BioLector – A new microbioreactor platform with continuous pH-control and substrate feeding**
*Dr. Frank Kensy and Dr. Christian Hetzel*, m2p-labs GmbH/Inc., Germany/USA
Today bioprocess development is mainly performed in lab-scale stirred tank bioreactors due to controlled process conditions provided by these reactors. Even if several microbioreactor concepts have been established so far in industry to fulfill the demand of high-throughput and ease of use, these technologies are mainly applied in clone screening and media development due to the lack of pH-control and feeding. Therefore, m2p-labs amplified the spectrum of their microbioreactor technology, BioLector®, towards pH-control and continuous feeding options. A user-friendly, disposable microfluidic bioreactor system was created that allows scalable, fully monitored and fully controlled fermentations at micro-scale.

11:00 – 11:30 **Speakers' photo then mid-morning break and poster exhibition and trade show**
*Please try to visit all the exhibition stands during your day at this event. Not only do our sponsors enable Euroscicon to keep the registration fees competitive, but they are also here specifically to talk to you.*

11:30 – 12:00 **Lyophilised Biopharmaceticals- Looking at Cake Properties**

*Dr Daryl R Williams*, Director of Development, Discovery Space and Reader in Particle Science, Department of Chemical Engineering, Imperial College, UK

An innovative method for the mechanical testing of freeze-dried biopharmaceutical cakes in situ vials has been developed. This simple and quick compression test allows a range of cake mechanical properties to be assessed quantitatively. It can be readily applied to fragile and moisture sensitive freeze-dried cakes within the vials. Freeze dried mannitol, sucrose and trehalose samples all yielded linear compressive elastic behavior for small strains with Young's Moduli of 25, 120 and 170 kPa respectively. This method discriminates readily between the three excipients reported here and can be used to optimise formulation of biopharmaceutical systems.

12:00 – 12:30 **Up-Scaling From A Micro- To A Lab-Scale Bioreactor By Applying The Fed-Batch Mode At Both Scales**

Csilla Török, *ACIB GmbH – Austrian Centre of Industrial Biotechnology; c/o University of Natural Resources and Life Sciences, A-1190 Vienna, Austria;* Monika Cserjan and Gerald Striedner*, Department of Biotechnology, University of Natural Resources and Life Sciences, A-1190 Vienna, Austria.*

12:30 – 13:30 **Lunch, poster exhibition and trade show**

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13:30 – 14:30 **Discussion session**

This discussion session is an informal question and answer session. This is an ideal opportunity to get advice and opinion from experts in this area. This session is not for questions about specific talks, which can be asked after the speakers session, but for discussing either general topics or specific issues.

There are three ways you can ask questions:

1. Before the session you can *submit your question to Euroscicon staff* at the registration desk,
2. Before and during the session you can *submit a question or comments, by email*, which will be provided on the day of the event
3. During the session you can *put your hand up* and join in

14:30 – 15:00 **ambr™ and ambr250™: advanced tools for automated optimization and process development in both microbial and cell cultures for application in biotherapeutics and industrial biotechnology**

*Mr Mwai Ngibuini,* Bioprocess product specialist, TAP Biosystems, UK

Exploration of a large number of cell lines or microbial strain candidates, as well as developing optimal process pathways requires the application DOE analysis with a suitable power number. Traditionally these campaigns require large laboratory space, and are both costly and labour intensive. TAP Biosystems has developed the advanced microbioreactor (ambr™) that is widely adopted as a rapid cell line selection and early stage cell culture optimization tool. As well as, the ambr250™, a tool that is being used for microbial strain selection, process optimization and late stage cell culture optimization. Here we present a technology overview and industry derived data.

15:00 – 15:30 **Afternoon Tea, last poster session and trade show**

15:30 – 16:00 **Introducing: micro-Matrix, the next generation in microbioreactors**

*Mr Martijn Kreukniet,* Product Manager, Applikon Biotechnology, UK

Applikon biotechnology specializes in development, manufacturing and marketing of bioreactor systems from production scale to laboratory scale. What are the trends and the challenges in the market when scaling down, what are the currently available solutions and where do we see the new developments take us? What is the current volume limit of the commercial small-scale bioreactors and why. Applikon offers systems down to 200 microliter volume. When scaling down to this volume the main process parameters should be maintained. Oxygen supply, mixing, nutrient supply are just a few parameters but also sample volume for proper analysis is important. Time to setup an experiment is another factor that will determine the success of a small-scale system. When a successful mini or micro bioreactor is developed and operational, the next challenge is to cope with the large amount of process data that will be generated by these systems. How can we make it easier to define multiple experiments and to interpret the experimental data. This presentation will aim to give an overview of the bioreactor market in general with a focus on the scale down market.

16:00 – 16:30 **Using an automated microscale processing approach for generation of scaleable design data**

*Dr Martina Micheletti,* Senior Lecturer, Biochemical Engineering UCL, London, UK

Coupling high throughput microscale techniques with the operation of automated laboratory platforms offer valuable opportunities in both upstream and downstream processing. The talk will show how the approach has been successfully applied to different scenarios, namely an industrial pharmaceutical process using Baeyer-Villiger monooxygenases for antibiotic synthesis and the optimisation of a protein refolding step from inclusion bodies. In both cases the microwell-based linked process sequence develop within the robotic platform enabled faster identification and characterisation of optimal conditions, showing good reproducibility over multiple runs and excellent scalability to larger scales of operation.

16:30 - 17:00 **Chairman's summing up**

**Registration Website**: http://www.regonline.co.uk/Mini2013

**About the Chair:**

**Chris Lowe's** group's primary research interest is in healthcare biotechnology, particularly where it is applied to the high-value low-volume sectors of biopharmaceuticals, sensors and diagnostics and microbial technology. The work is highly multidisciplinary and not only covers aspects of molecular biology, biochemistry, microbiology, chemistry, physics, electronics and engineering, but also the entire range from fundamental science to strategic and applied science, much of which has significant commercial application.

**About the Speakers:**

**Galip Akay** holds the established chair of Chemical Engineering at Newcastle University. He has a multi-disciplinary education and research background both in academia and industry. He is one of the founders of Process Intensification in chemical technology. More recently, he extended this discipline to biotechnology, tissue engineering and agriculture through the discovery of the 'confinement phenomenon'. His research in energy and materials science is commercialised by 3 spin-out companies in collaboration with international companies. He has some 250 publications and over 70 patents. He is a founding trustee of the UK Children's Neurological Research Campaining.

**Frank Kensy** studied Biochemical Engineering at the University Essen, Madrid and at RWTH Aachen. After receiving his diploma, he first started his professional career as fermentation scientist
for new recombinant enzymes and pharmaceutical proteins at Rhein Biotech N.V. in Düsseldorf.
In 2002 he decided to return to RWTH Aachen University for doing his PhD on shaken microbioreactors with Prof. Jochen Büchs. Since November 2005 he is founder and managing director of m2p-labs responsible for R&D and sales.

**Daryl R. Williams** has a B.Sc.(Hons) from University of Melbourne, Australia, a M.Sc. from Lehigh University, USA before completing his Ph.D at Imperial College London where he is the Reader in Particle Science. Daryl has published over 70 journal papers, has 5 patents and is a world leader in advanced instrumental characterisation of solids. He is the founder of Surface Measurement Systems. He researches the surface/bulk characterisation of organic solids including biopharmaceutics, as well as their manufacture using spray and freeze drying, crystallisation, freeze drying, milling and granulation. Sponsors include EPSRC, BBSRC, Pfizer, Astra-Zeneca, P&G, BTL, Avecia and GSK.

**Mwai Ngibuini** is the ambr250 bioprocess product specialist at TAP Biosystems, prior to joining TAP Mwai had over ten years upstream bioprocessing experience working in both biopharm and industrial biotechnology where he worked with a wide range of microbial strain. Mwai Ngibuini completed a BEng in Chemical engineering at London South Bank University and then studied for an MSc in Biochemical engineering at University College London graduating at 2003. His area of interest is Bioreactor technology.

**Martijn Kreukniet** is a product manager at Applikon Biotechnology B.V. in Delft, the Netherlands. He received his bachelor degree in Biotechnology at the Rotterdam University in 2000 and has since been involved in field of industrial biotechnology. His work at Applikon and natural interest to know more, has given him a broad knowledge in the field of sensor technologies and small-scale bioreactors.

**Martina Micheletti** obtained her first degree in Chemical Engineering and a PhD in Fluid Mechanics in Bioreactors from King's College London. After a 3 years postdoctoral position in the Biochemical Engineering department at UCL she was appointed Lecturer in the same department in 2007. Her research focuses on the study of the influence of the engineering environment on different types of biological organisms in upstream and downstream bioprocessing operations with the aim to address key challenges in the scale-up of pharmaceutical processes. In particular she has published her work on the use of automated microscale processing approaches to speed up bioprocess development steps.

## POSTER PRESENTATIONS

### NOVEL FLUOROPOLYMER MICROFLUIDICS FOR RAPID IMMUNOASSAYS

A.I. Barbosa[1], A.P. Castanheira[2], A.D. Edwards[3] and N.M. Reis[1]. *[1]Department of Chemical Engineering, Loughborough University, Loughborough LE11 3TU, UK, [2]Capillary Film Technology Ltd, Daux Road, West Sussex RH14 9SJ, UK, [3]Reading School of Pharmacy, University of Reading, Whiteknights, Reading RG6 6AP, UK*

There is an increasing trend in >$100M life science ELISA market for simultaneous detection of multiple biomolecules from a single biological sample – a technique called multiplex detection. A new disposable device based on fluoropolymer microfluidic capillary technology[1, 2] will be presented which combines the sensitivity of standard laboratory immunoassays with the large surface-to-volume-ratio of microcapillaries, providing an affordable and miniaturised multiplex ELISA detection device. The device is assembled by incorporating a multiplex test strip, push-fit seals, and a flow interface/system (e.g. syringe or pipette). The test strips consist of 10 x 200 µm bore microcapillaries embedded in parallel in a transparent fluoropolymer ribbon. Together with a flatbed scanner, the microfluidic capillary platform/device was used for the detection and quantitation of prostate cancer biomarker (PSA) and human cytokines in a singleplex and multiplex system. Immunoassays performed in the capillary film platform using commercial colorimetric sandwich ELISA reagents have observed limit of detection (LOD) of 0.9375 ng/ml for prostate specific antigen (PSA) and 10-60 pg/ml for hIL-1beta, hIL-6, hIL-12 and TNF-alpha inflammatory cytokines, typically with CVs ≤ 10% in 15 minutes. This shows it is possible to successfully miniaturise and speed up commercial heterogeneous, sensitive microtiter plate (MTP) sandwich ELISA chemistry used by diagnostic labs to the fluoropolymer microfluidic device. The new microfluidic capillary platform offers a novel affordable approach to rapid, quantitative and multiplex immunoassays with a broad range of applications in a lab setting and point-of-care testing for quantitation of biomarkers and other macromolecules.

References:

1. Reis, Edwards, Slater, Mackley, Patent application WO/2011/117579 (published 23rd March 2011)
2. A. D. Edwards, N. M. Reis, N. K. H. Slater and M. R. Mackley, A simple device for multiplex ELISA made from melt-extruded plastic microcapillary film,
Lab on a Chip, 11, 4267-4273 (2011)

### BIOPROCESS MINIATURIZATION DEVELOPMENT AND OPTIMIZATION. SPECIAL FEATURES OF THE PROCESS OF OBTAINING AND THE CHARACTERISTIC OF THE RECOMBINANT ANALOG OF INTERFERON OF THE GAMMA

G.M. Levagina, Y.S Gogina., L.R Lebedev., V.I. Masycheva, G.M Sysoyeva., E.D. Danilenko. *Federal budgetary establishment of science the State scientific center virology and biotechnology "Vector", Institute of the medical biotechnology (IMBT FBUN GNTS WB "Vector") Russia*

Recombinant human Gamma-interferon (rchIFN-γ) is protein with molecular weight about 17 kDa, possessing significant antitumorigenic, antipyretic and antiviral action, which makes its application in medicine completely promising. With obtaining of rchIFN-γ necessary to introduce into the diagrams of cleaning the stage of denaturing and renaturatsii of protein, since with the microbial synthesis of rchIFN-γ it is accumulated in the form undissolved aggregates, so-called. "the corpuscles of start", which leads to considerable reduction in the output of end product, and also increase in the prime cost of preparation because of the significant temporary and material expenditures. In FBUN GNTS WB "Vector" was created the analog of rchIFN-γ – deltaferon. The recombinant analog of human interferon-gamma - deltaferon is the protein, synthesized shtamom of E.coli MH1, which contain the plasmid of pIFN Δ 10, which is build it the gene of interferon- gamma person, with the deletion of 10 C- end codons and the replacement Arg129 to Gly, Lys130 to Ser and Arg131 to Ala. As a result this modification in the molecules of the analog of rchIFN-γ - of deltaferona appeared a number of the distinguishing features, such as stability to the proteolysis and biosynthesis in the prokaryotic cells in the dissoluble form. Is developed the preparative method of obtaining deltaferona, which guarantees high output and high value of the surface finish of preparation just as its stability in the process of storage. Were carried out comparative studies of the biological functions of rchIFN-γ and deltaferona. Retention in deltaferona of anti-proliferating activity characteristic for the the initial of rchIFN-γ they observed in the mononuclear cells of man, where it was shown that the proteins to the equal degree decreased the proliferation of cells. On the experimental model of adjuvant arthritis of mice, caused by the intracutaneous introduction of complete Freund's adjuvant (PAF), it was established, that deltaferon in the level of antipyretic activity essentially did not differ from rchIFN-γ.

**MICROBIOREACTOR SCREENING OF ENGINEERED *E.coli* K4 STRAINS FOR INCREASED PRODUCTION OF CHONDROITIN-LIKE CAPSULAR POLYSACCHARIDE**

D. Cimini, A. Alfano, E. Carlino, O. Argenzio, K. Della Corte, C. Schiraldi. *Department of Experimental Medicine, Section of Biotechnology and Molecular Biology, Second University of Naples, via de Crecchio 7, 80138 Napoli, Italy*.

A growing world market of billion dollars per year regards molecules such as hyaluronic acid, heparin, and chondroitin sulphate (CS) that are among the top ranked products in industrial biotechnology for biomedical applications. Chondroitin sulfate is currently used as nutraceutical for the treatment of osteoarthritis, and several new therapeutic applications are under evaluation. In this respect the bacterium *E.coli* K4 is a potential natural source of CS precursor since it produces a capsule whose structure resembles that of CS. *E.coli* K4 is therefore currently used by our group as host for the development of engineered strains with a higher production of capsular polysaccharide. The potential of all strains is analysed in microbioreactor batch experiments that allow the establishment of well controlled fermentation conditions and the attainment of results that are reproducible on the 2.5L scale.

**UP-SCALING FROM A MICRO- TO A LAB-SCALE BIOREACTOR BY APPLYING THE FED-BATCH MODE AT BOTH SCALES**

Csilla Török, *ACIB GmbH – Austrian Centre of Industrial Biotechnology; c/o University of Natural Resources and Life Sciences, A-1190 Vienna, Austria;* Monika Cserjan, Gerald Striedner*; Department of Biotechnology, University of Natural Resources and Life Sciences, A-1190 Vienna, Austria;*

Micro-bioreactors are established for strain screening and bioprocess development, but the up-scaling from the micro- to the lab-scale is not straightforward. The cultivation conditions in the micro-scale differ from those in the lab-scale. These conditions, such as, the medium composition, the cultivation mode (batch, fed-batch, continuous) or the oxygen supply, influence the microbial growth. As a consequence, a strain might show different growth and product formation characteristics at different scales. This influences the strain selection and the process development. One way to overcome the limitation of different growth conditions at different scales is to mimic the conditions of the large scale in the small scale process. Therefore, we have established a cultivation protocol for the BioLector micro-bioreactor system (m2p-labs), which enables us to cultivate *Escherichia coli* strains under conditions close to those in a lab scale bioreactor, but in higher throughput. We mimic the carbon-limited growth conditions, which are present in large scale fed-batch processes, with a medium based on enzymatic glucose release (m2p-labs). Thereby, we are able to cultivate different *E. coli* strains at defined growth rates and to control the growth rate by using different amounts of the glucose releasing enzyme. With our protocol we observe no oxygen limitation, the pH value is in a range between 5.5 and 7.0 and we reach cell densities of up to 14 g/l. Applying this protocol we cultivated three industrial relevant *E. coli* strains in the BioLector and compared the growth behaviour in the BioLector to the behaviour in high cell density lab-scale fermentations. In the fully controlled fermentation we used a standard synthetic medium composition and an exponential substrate feed. Despite the different media we observed that strain specific growth characteristics, like biomass yield and acidification pattern are comparable between scales. The strain with the highest yield coefficient ($Y_{X/S}$) in the BioLector cultivation is the strain with the highest yield coefficient in the lab scale fermentation. The ammonia consumption in the lab scale process reflects the course of the pH value in the BioLector cultivation. In addition, when we expressed a recombinant protein, the strain with the highest product yield in the BioLector was also the strain showing the highest productivity in the larger scale. The expression patterns are transferable. In conclusion, our protocol with a medium facilitating enzymatic glucose release allows us to cultivate different *E. coli* strains in a mico-bioreactor system under conditions comparable to those in the large scale. The growth and product formation kinetics in the micro-sale are transferable to the larger scale but the micro-bioreactor increases the possible cultivation throughput.

**THE USE OF HIGH THROUGHPUT TECHNOLOGY FOR IMPROVING AND ACCELERATING VACCINE PRODUCTION PROCESS DEVELOPMENT**

V. Le Bras[1]*, A. Morreale[1], M. Tellier[1], M. Coppi[1], M. Lanero[1], F. Bernuzzi. *[1] GSK Vaccines; * GSK 89 Rue De L'Institut, Rixensart, B1330, Belgium*

Traditionally industrial fermentation process development for new vaccines is conducted in 10 to 20-L scale bioreactors, presenting similar characteristics compared to the final scale ones. This type of approach is time consuming and represents a significant cost in terms of resources and raw materials. This means that the number of trials performed per week is limited. As a result sub-optimal shortcuts are taken during the development, to quickly find a functional process. We will see that the micro-bioreactor technology may be a convenient vehicle to more deeply explore two aspects that are usually less studied during vaccine process development: clone and media screening. Usually, due to equipment and/or timing limitations, only one bacterial (or yeast) transformant producing a certain antigen is used for developing a high cell density process in bioreactor, assuming all clones are identical based on a very limited screening in flask cultures. Of course, prior to development, this particular clone is tested for growth capability and antigen production. But, how can we be sure that we are not missing a super producer among the, let's say, 100 colonies resulting from a transformation? In other words, when you have the agar plate in front of you, why choose this clone and not the one just beside? Only because it looks good? Starting with the best available clone in order to develop a performing fermentation process could give a definitive advantage in the success of a future vaccine development. A high throughput fermentation technology is then necessary to facilitate the screening of a large number of clones in a single experiment. In this presentation we report the evaluation of the Biolector micro bioreactor. One of the major challenges was to standardize the inoculums in terms of quantity and quality (physiological state). For instance, colonies arising from transformation show large variation in size. A pre-culture step with glucose-limited growth (enzymatic release) was evaluated to slow down and synchronize the growth of the colonies and minimize physiological variations, before transfer to the actual culture step including both growth and expression phases. A screening protocol was developed for pre-culture and culture steps, critical parameters (DO – Biomass – pH) were monitored online. Results analysis allowed the identification of the best clone for further fermentation process development. Once the best available clone has been selected, the fermentation process still needs to be optimized. One key parameter is the culture medium, however due to the limited number of possible runs, optimization of the culture medium usually consists of starting with a complete medium, and if needed only working on the components which are historically known to be tricky. In this context micro-bioreactors can help by evaluating simultaneously numerous different media. A methodology for screening supplementation in a Chemically Defined Medium (CDM) for optimizing microorganism cultivation was established. This methodology was applied to assess the impact of the supplementation of 18 different amino acids to a basic chemically defined medium for growth of *E. coli*. The experimental design was determined using Design of Experiments (DoE) Methodology and evaluated 40 different media in addition to the basic medium (repeated 8 times). Media were prepared using a robotic liquid handling system (TECAN technology). Cultures were cultivated using a Biolector micro-bioreactor. Finally Amino acids having a significant impact (positive or negative) on monitored parameters could be statistically determined. This screening design was tested with two different *E. coli* strains, in two different Biolector runs. Growth profiles were highly reproducible (intra and inter runs) and statistical analysis quantified the impact of an amino acid supplementation (alone or in combination) on *E. coli* cultures. Further analysis should be done by studying growth profile (OD, pH), growth kinetic ($\mu$, $\mu_{max}$) and productivity. To conclude, Micro-bioreactors technology can be used as a complement to traditional bioreactors during process development, offering a chance to assess additional options like the choice of the transformant or impact of media components, without negatively impacting the timelines by allowing the evaluation of multiple factors in parallel.

**MICROFABRICATION OF ENZYMATIC BIOFUEL CELLS AS POWER SOURCE FOR HEALTHCARE DEVICES**

Mirella Di Lorenzo. *Department of Chemical Engineering, University of Bath*

Enzymatic Biofuel Cells (EBFCs) are promising power sources that can be employed in the human body. These electrochemical devices are capable of converting the sugars present in blood into useful energy at high energy density. high specificity of enzymes, can lead to light and compartment-less devices, which are easy to miniaturize. The Nonetheless, the process of miniaturization of EBFCs is still in its infancy and many challenges need to be overcome for practical applications such as medical implants. The development of functional high surface enzyme-immobilized microelectrodes is in particular key.We have developed a miniature glucose/oxygen EBFC that implements glucose oxidase (GOx) and laccase (LAC) as biocatalysts respectively at the anode and at the cathode.The microelectrodes were made of highly porous gold (hPG), and were produce by directly electroplating a hPG film onto the surface of gold micro-electrodes fabricated by lift-off lithography. GOx was then electrochemically adsorbed onto the hPG surface, while LAC was chemically bounded by functionalising the hPG surface with amino groups.Preliminary results showed that the EBFC was able to produce a peak power density of 3 μW $cm^{-2}$at a potential of 0.2 V.The device was run in continuous mode and no external mediators were added to the system to assist the electron transfer process from the GOx redox centre to the hPG electrode.

**STEM CELL BASED TRANSPLANTATION STRATEGIES FOR PERINATAL SUB CORTICAL REMYELINATION**

Crystal Ruff[1], Hui Ye[1], Natasha Stribbell[1], Jean Legasto[1], Jian Wang[1], Liang Zhang[2], Michael Fehlings[1]
*[1] Division of Genetics and Development, Department of Surgery, Toronto Western Research Institute (TWRI), University Health Network (UHN), [2] Division of Fundamental Neurobiology, Department of Medicine, TWRI, UHN*

Hypothesis and Purpose: Cerebral Palsy (CP) is the most common neurodevelopmental disorder, affecting 2.5/1000 live births. It is characterized by demyelination, motoneuron cell death and subsequent neuromotor impairment. Neural stem and progenitor cells (NSPCs) show great potential for cellular replacement and remyelination in models of sub-cortical injury and dysmyelination. However, it is currently unknown whether transplantation is effective at the most clinically relevant disease time points – which commonly follow age-dependent immune privilege. This study investigates the capacity for both adult and pluripotent stem cell-derived NSPCs to functionally remyelinate the sub-cortical white matter, prior to neuronal cell loss, as a treatment strategy for CP. Methods: NSPCs derived from the sub-ventricular zone of YFP+ transgenic animals, were injected bilaterally into the anterior and posterior aspects of the anlagens of the corpus callosum and cerebellar peduncle. Animals were injected, using a pulled glass needle, on P0, P7 (equivalent to human birth) and P21 (equivalent to ~2 years human age) in the shiverer mouse model, which genetically lacks compacted myelin. They survived for 45 days, with or without immune ablation. Results and Conclusions: Cells integrated anatomically, dependent on immune status, into the corpus callosum, periventricular areas and fimbria of the hippocampus preferentially, and became Olig2+, MAG+,MBP+, GFAP- oligodendrocytes, which enwrapped NF200+ axons. aNPC-mediated myelination restored ion channel profiling, and normalized *ex vivo* compound action potential, activation threshold, refractoriness and response to ischaemia. This provides the first evidence that these aNPCs can functionally incorporate into disordered CNS and shows their promise for future clinical extension.

Keywords: bioreactor, micro, automated, culture, single use, Microbioreactors, Well Plate, Liquid Feed, bioprocesses, fermentation, cell culture, miniature bioreactor, Antibiotics, Bio-microreactors, Bio-Process Intensification, Enzymes, Fermentation, lyophilisation, biopharmaceuticals, Freeze drying, mechanics, formulation, High through put, scalability, automation, single use, bioreactors, small scale, bioreactor, miniaturization,scale down model, parallel bioprocesses, screening, downscaling, micro fermentation, micro bioreactor, microwell, bioprocessing, biocatalysts, refolding, inclusion bodies.

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