（高坂委員提出資料）　　（参考３）

ヒト胎児幹細胞を用いた前臨床研究について

Dr. Svendsens group (USA)

J Comp Neurol. 2004 Jul 19;475(2):211-9.

Human neural stem cell transplants improve motor function in a rat model of Huntington's disease.

McBride JL, Behrstock SP, Chen EY, Jakel RJ, Siegel I, Svendsen CN, Kordower JH.

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The present study investigated the neuroanatomical and behavioral effects of human stem cell transplants into the striatum of quinolinic acid (QA)-lesioned rats. Twenty-four rats received unilateral QA (200 nM/microl) injections into the striatum. One week later, rats were transplanted with stem cells derived from human fetal cortex (12 weeks postconception) that were either 1) pretreated in culture media with the differentiating cytokine ciliary neurotrophic factor (CNTF; n = 9) or 2) allowed to grow in culture media alone (n=7). Each rat was injected with a total of 200,000 cells. A third group of rats (n=8) was given a sham injection of vehicle. Rats transplanted with human stem cells performed significantly better over the 8 weeks of testing on the cylinder test compared with those treated with vehicle (P < or = 0.001). Stereological striatal volume analyses performed on Nissl-stained sections revealed that rats transplanted with CNTF-treated neurospheres had a 22% greater striatal volume on the lesioned side compared with those receiving transplants of untreated neurospheres (P = 0.0003) and a 26% greater striatal volume compared with rats injected with vehicle (P < or = 0.0001). Numerous human nuclei-positive cells were visualized in the striatum in both transplantation groups. Grafted cells were also observed in the globus pallidus, entopeduncular nucleus, and substantia nigra pars reticulata, areas of the basal ganglia receiving striatal projections. Some of the human nuclei-positive cells coexpressed glial fibrillary acidic protein and NeuN, suggesting that they had differentiated into neurons and astrocytes. Taken together, these data demonstrate that striatal transplants of human fetal stem cells elicit behavioral and anatomical recovery in a rodent model of Huntington's disease.

PMID: 15211462 [PubMed - indexed for MEDLINE]

キノリン酸障害ラットに対し、週齢 12 週のヒト胎児皮質より由来幹細胞を移植したところ、対照群に比較して術後８週間に渡って運動機能の改善を認めた。組織学的検討を行ったところ、幹細胞移植側の線条体容積は対照群と比較して有意に 26%増加していた。ハンチントン病のげっ歯類モデルに対する、線条体領域へのヒト胎児幹細胞の移植は、行動学的及び解剖学的な回復を導いた。

J Neurosci Res. 2004 Apr 15;76(2):174-83.

Improving the survival of human CNS precursor-derived neurons after transplantation.

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We have examined the effects of predifferentiation and energy substrate deprivation on long-term expanded human neural precursor cells (HNPCs). The pre-differentiation of HNPC cultures produced large numbers of neurons (>60%) and mature glial cells capable of generating glycogen stores that protected the neuronal population from experimental metabolic stress. When predifferentiated HNPCs were transplanted into intact adult rat hippocampus, fewer cells survived compared to undifferentiated HNPC transplants. This cell death was completely attenuated, however, when predifferentiated HNPC cultures were pretreated to boost glial energy stores and resulted in greatly increased neuronal survival in vivo. The transplanted cells primarily engrafted within the granular layer of the dentate gyrus, where a large proportion of the predifferentiated HNPCs co-expressed neuronal markers whereas most HNPCs outside of the neuronal layer did not, indicating that the predifferentiated cells remained capable of responding to local cues in the adult brain. Undifferentiated HNPCs migrated more widely in the brain after grafting than did the predifferentiated cells, which generally remained within the hippocampus.

PMID: 15048915 [PubMed - indexed for MEDLINE]

ヒト神経前駆細胞(HNPCs)の predifferentiation とエネルギーサブストレートについて検討した。predifferentiation HNPCs はグリコーゲン蓄積能を有する多くのニューロンを産生した。predifferentiation HNPCs を成体ラット海馬へ移植したところ、未分化 HNPCs よりも残存率は低かった。predifferentiation HNPCs の残存率は、グリア細胞のエネルギー蓄積を増幅する処置を施すことで向上した。移植細胞は、神経層の外にある HNPCs の大部分と反対に、歯状回の顆粒層に生着し、多くの predifferentiation HNPCs はニューロンマーカーを呈示しており、このことは predifferentiation 細胞が成体脳のローカルキューへの反応性を保持することを示唆した。未分化 HNPCs は移植後、脳のより広範に分布していた。

Dr. Bradfords Group (UK)

Keio J Med. 2002 Sep;51(3):148-53.

The use of foetal human brain tissue as brain implants: phenotype manipulation by genetic manipulation and biochemical induction.

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The use of dopaminergic mesencephalic (VM) human foetal brain tissue as implants to neurosurgically treat Parkinson's disease has been in progress since the 1980's. A major limitation in the use of VM tissue is the amount of tissue available from each human embryo. Usually tissue from about 7 embryos is required to treat each patient unilaterally. To overcome this we have developed various strategies. One is to convert embryonic cerebral cortex in human embryos into dopaminergic tissue which is stable, and which will secrete dopamine in vivo once implanted. The cerebral cortex is about 500 times larger than the VM and can therefore provide a lot more tissue for transplantation. This can be achieved by genetic manipulation of the embryonic cerebral cortex tissue, involving the lipo-transfection of multiple copies of the human tyrosine hydroxylase gene into both neurones and glial cells. In another approach we have biochemically manipulated the development of the cerebral cortex to direct the neurotransmitter phenotype towards the dopaminergic type, and away from other phenotypes. This tissue, too, is stable and will synthesise and secrete dopamine when transplanted. Our third approach has been to manipulate pluripotential neural cells which are yet to develop into neurones and glial cells. These cells can be expanded in number many-fold before treatment to direct their development into stable dopaminergic neurones in large numbers (70%), which synthesise and release dopamine. When used as transplants in animal models of Parkinson's disease, these various types of artificially induced dopaminergic tissue are very effective at reducing the Parkinsonian syndrome.

PMID: 12371646 [PubMed - indexed for MEDLINE]

ドパミン作動性(VM)中脳ヒト胎児組織の移植が 1980 年代より進められているが、一回の治療に 7 体の胎児が必要である。この問題を克服するため、①ヒト胚大脳組織を遺伝子操作により、チロシン水酸化酵素遺伝子の複数コピーを導入して、ドパミン作動性組織に転換することで、VM の 500 倍の大きさとし、細胞不足を克服する方法、②大脳皮質の神経伝達物質表現型をドパミン作用性に導くよう発生過程を生化学的に操作する方法、③ニューロンあるいはグリア細胞への多分化能を有する神経細胞を操作する方法、について検討した。いずれもパーキンソン症状の改善に有用と考えられた。

Brain Res Dev Brain Res. 2002 May 30;136(1):27-34.

The controlled conversion of human neural progenitor cells derived from foetal ventral mesencephalon into dopaminergic neurons in vitro.

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The expansion and differentiation of neural progenitor cells in vitro provides an approach to study the development and differentiation of neurons. The ventral mesencephalic area of the brain is an important source of neural progenitor cells and the differentiated neural progenitor cell has paramount potential for use in transplant therapies such as those used in the treatment of neurodegenerative diseases. Here, the controlled conversion of human foetal progenitor cells derived from ventral mesencephalon into dopaminergic neurons is reported. The immunoreactivity to tyrosine hydroxylase (TH) and levels of dopamine (DA) and its metabolite, 3,4-dihydroxyphenylacetic acid (DOPAC), secreted into culture medium, were used to assess dopaminergic neuronal phenotype. Expansion of the neural progenitor cells for 3 weeks in the presence of basic fibroblast growth factor (2 ng/ml) followed by its withdrawal resulted in approximately 60% of cells staining positive for TH, when challenged in concert with brain-derived neurotrophic factor (50 ng/ml), DA (10 microM) and forskolin (10 microM) for a further 3 weeks. A corresponding 41-fold increase in DA and DOPAC was measured in the incubation medium by HPLC. Therefore, the successful conversion of human foetal progenitor cells in vitro resulting in the desired dopaminergic neuronal phenotype, could provide a solution to the problem of limited availability of human foetuses for clinical surgical transplantation therapies, which are currently in progress for the treatment of neurodegenerative diseases such as Parkinson's disease.

PMID: 12036514 [PubMed - indexed for MEDLINE]

中脳腹側は神経変性疾患に対する神経前駆細胞等の供給源として有用と考えられ、ここより分離されたヒト胎児前駆細胞を塩基性線維芽細胞成長因子単独の存在下で、次に神経栄養因子、ドパミン、フォルスコリン存在下で培養したところ、60%がドパミン作動性を示した。培養中、ドパミンとその代謝物質が 41 倍になっていた。以上の結果は、パーキンソン病等の細胞治療にとって、入手可能なヒト胎児が限られるという問題を解決するものである。

Dr. Kims group (Canada/Korea)

Neurosci Res. 2003 Oct 15;74(2):266-77.

Brain transplantation of genetically engineered human neural stem cells globally corrects brain lesions in the mucopolysaccharidosis type VII mouse.

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In the present study, we investigated the feasibility of using human neural stem cells (NSCs) in the treatment of diffuse central nervous system (CNS) alterations in a murine model of mucopolysaccharidosis VII (MPS VII), a lysosomal storage disease caused by a genetic defect in the beta-glucuronidase gene. An immortalized NSC line derived from human fetal telencephalon was genetically engineered to overexpress beta-glucuronidase and transplanted into the cerebral ventricles of neonatal MPS VII mouse. Transplanted human NSCs were found to integrate and migrate in the host brain and to produce large amount of beta-glucuronidase. Brain contents of the substrates of beta-glucuronidase were reduced to nearly normal levels, and widespread clearing of lysosomal storage was observed in the MPS VII mouse brain at 25 days posttransplantation. The number of engrafted cells decreased markedly after the transplantation, and it appears that the major cause of the cell death was not the immune response of the host but apoptotic cell death of grafted human NSCs. Results showed that human NSCs would serve as a useful gene transfer vehicle for the treatment of diffuse CNS lesions in human lysosomal storage diseases and are potentially applicable in the treatment of patients suffering from neurological disorders. Copyright 2003 Wiley-Liss, Inc.

PMID: 14515356 [PubMed - indexed for MEDLINE]

βグルクロニダーゼ遺伝子欠損によるリソソーム蓄積で発症するムコ多糖症 VII 型のモデルマウスに対して、ヒト神経幹細胞(NSCs)投与の効果を検討した。ヒト胎児終脳に由来する NSC を不死化し、βグルクロニダーゼを過剰発現するよう遺伝子操作し、モデルマウスの脳室に移植した。その結果βグルクロニダーゼ値は一旦増加の後に正常化し、移植後 25 日目にはリソソームの除去が認められた。その後移植細胞は減少したが、これは免疫反応ではなくアポトーシスのようであった。ヒト NSC はリソソーム蓄積症の治療において、有効な遺伝子導入手法となりうる。

Stroke. 2003 Sep;34(9):2258-63. Epub 2003 Jul 24.

Human neural stem cell transplantation promotes functional recovery in rats with experimental intracerebral hemorrhage.

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BACKGROUND AND PURPOSE: Cell transplantation has been used to reduce behavioral deficit in cerebral ischemia. However, there is no report about cell transplantation in experimental intracerebral hemorrhage (ICH). We hypothesize that intravenously transplanted human neural stem cells (NSCs) can migrate and differentiate into neurons or glial cells, thereby improving functional outcome in ICH. METHODS: Experimental ICH was induced by intrastriatal administration of bacterial collagenase in adult rats. One day after surgery, the rats were randomly divided into 2 groups to receive intravenously either immortalized Lac z-positive human NSCs (5x10(6) cells in 500 microL, n=12) or the same amount of saline (n=13). The animals were evaluated for 8 weeks with modified limb placing and rotarod tests. Transplanted NSCs were detected by X-gal histochemistry or beta-gal immunohistochemistry with double labeling of GFAP, NeuN, neurofilament, or CNPase. RESULTS: Intravenously transplanted NSCs migrated selectively to the perihematomal areas and differentiated into neurons (approximately 10% of beta-gal+ cells) and astrocytes (approximately 75%). The NSC-transplanted group showed better functional performance on rotarod test after 2 weeks and on modified limb placing test after 5 weeks compared with the control group ($P<0.05$), and these effects persisted for up to 8 weeks. There was no difference in the final hemispheric area between the 2 groups. CONCLUSIONS: Intravenously transplanted NSCs can enter the rat brain with ICH, survive, migrate, and improve functional recovery. Transplantation of human NSCs can be used to restore neurological deficits in experimental ICH.

PMID: 12881607 [PubMed - indexed for MEDLINE]

脳出血に対する細胞療法として、ヒト神経幹細胞(NSCs)の静注により、幹細胞がニューロン及びグリア細胞に分化し予後を改善する可能性について検討した。脳内出血を誘発したラットを、NSCs 投与群、生理食塩水投与群に分け評価した。免疫組織学的に NSCs の局在を評価したところ、NSCs は血腫辺縁領域に移動し、ニューロンと星状細胞に分化していた。機能評価では対照群に対して有意な改善を示し、効果は最高 8 週間持続した。静注によるヒト NSCs の移植は、脳出血に対して機能的改善をもたらすことが示唆された。

J Neurosci Res. 2004 Oct 15;78(2):215-23.

Human neural stem/progenitor cells, expanded in long-term neurosphere culture, promote functional recovery after focal ischemia in Mongolian gerbils.

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Transplantation of human neural stem cells (NSCs) is a promising potential therapy for neurologic dysfunctions after the hyperacute stage of stroke in humans, but large amounts of human NSCs must be expanded in long-term culture for such therapy. To determine their possible therapeutic potential for human stroke, human fetal neural stem/progenitor cells (NSPCs) (i.e., neurosphere-forming cells) were isolated originally from forebrain tissues of one human fetus, and expanded in long-term neurosphere culture (exceeding 24 weeks), then xenografted into the lesioned areas in the brains of Mongolian gerbils 4 days after focal ischemia. Sensorimotor and cognitive functions were evaluated during the 4 weeks after transplantation. The total infarction volume in the NSPC-grafted animals was significantly lower than that in controls. Approximately 8% of the grafted NSPCs survived, mainly in areas of selective neuronal death, and were costained with antibodies against neuronal nuclei antibody (NeuN), microtubule associated protein (MAP-2), glial fibrillary acidic protein (GFAP), and anti-2'3' cyclic nucleotide 3'-phosphodiesterase (CNPase). Synaptic structures between NSPCs-derived neurons and host neurons were observed. Furthermore, gradual improvement of neurologic functions was observed clearly in the NSPC-grafted animals, compared to that in controls. Human NSPCs, even from long-term culture, remarkably improved neurologic functions after focal ischemia in the Mongolian gerbil, and maintained their abilities to migrate around the infarction, differentiate into mature neurons, and form synapses with host neuronal circuits. These results indicate that in vitro-expanded human neurosphere cells are a potential source for transplantable material for treatment of stroke.

ヒト神経幹細胞(NSCs)移植は脳卒中の超急性期に対する潜在的治療法であるが、多くの NSCs を得るには長期の培養が必要である。そこでヒト胎児由来神経幹／前駆細胞(NSPCs)＝ニューロスフェア形成細胞を、ヒト胎児前脳より採取、24 週以上培養し、虚血後スナネズミ脳に移植した。知覚運動機能と認知機能を移植後 4 週間にわたり評価したところ、NSPCs 移植群では梗塞領域が縮小しており、約 8% の NSCPs が細胞死領域で、ニューロンへ分化していた。宿主のニューロンと移植片のニューロンにはシナプス構造が認められた。また対照群と比較して神経学的機能の改善も認めた。ヒト NSPCs は長期培養を経ても神経機能改善をもたらし、脳卒中に対する移植細胞のソースとして有用であることが示唆された。

J Neurosci Res. 2005 Apr 15;80(2):182-90.

Transplantation of human neural stem cells for spinal cord injury in primates..

Iwanami A, Kaneko S, Nakamura M, Kanemura Y, Mori H, Kobayashi S, Yamasaki M, Momoshima S, Ishii H, Ando K, Tanioka Y, Tamaoki N, Nomura T, Toyama Y, Okano H.
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Recent studies have shown that delayed transplantation of neural stem/progenitor cells (NSPCs) into the injured spinal cord can promote functional recovery in adult rats. Preclinical studies using nonhuman primates, however, are necessary before NSPCs can be used in clinical trials to treat human patients with spinal cord injury (SCI). Cervical contusion SCIs were induced in 10 adult common marmosets using a stereotaxic device. Nine days after injury, in vitro-expanded human NSPCs were transplanted into the spinal cord of five randomly selected animals, and the other sham-operated control animals received culture medium alone. Motor functions were evaluated through measurements of bar grip power and spontaneous motor activity, and temporal changes in the intramedullary signals were monitored by magnetic resonance imaging. Eight weeks after transplantation, all animals were sacrificed. Histologic analysis revealed that the grafted human NSPCs survived and differentiated into neurons, astrocytes, and oligodendrocytes, and that the cavities were smaller than those in sham-operated control animals. The bar grip power and the spontaneous motor activity of the transplanted animals were significantly higher than those of sham-operated control animals. These findings show that NSPC transplantation was effective for SCI in primates and suggest that human NSPC transplantation could be a feasible treatment for human SCI.

近年の研究により、成体ラット脊髄損傷モデルへ至適な時期に神経幹・前駆細胞を移植することが有効であることが示されているが、本研究では、ヒト脊髄損傷患者を対象とした神経幹・前駆細胞移植の臨床治験を始める前に霊長類の脊髄損傷モデルを用いた前臨床的な検討が必要であると考え、10匹の成体コモンマーモセットの頚随損傷モデルを作成し、その内ランダムに選択した5匹に、損傷後9日目に試験管内で増幅したヒト胎児脊髄由来神経幹・前駆細胞を移植し、残り5匹には細胞培養の培地のみを移植し、シャム手術対照群とした。神経幹・前駆細胞移植群と対照群につき、握力と自発運動能を指標とした運動機能を評価したところ、神経幹・前駆細胞移植群においては、シャム手術対照群と比較して有意に運動機能が改善していることが明らかとなった。また、移植したヒト神経幹・前駆細胞が、マーモセット脊髄内でニューロン、アストロサイト、オリゴデンドロサイトに分化していることが確認されている。これらの所見は、霊長類脊髄損傷モデルにおいて神経幹・前駆細胞移植が有効な治療法であり、神経幹・前駆細胞移植がヒト脊髄損傷の治療法として有望であることを示している。

（岡野委員提出資料）　　（参考４）

Regulatory Oversight of Clinical Development Programs for Spinal Cord Injury: an FDA Perspective

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FDA/CBER Regulates Human Cells, Tissues, Cellular and Tissue-Based Products (HCT/Ps)

Selected Examples of How HCT/Ps Are Regulated

- Regulated as drugs, biologics or devices
  - Manipulated cells/tissue
  - Genetically modified cells
  - Non-homologous use of cells or tissues
  - Cells/tissues combined with drugs, devices biologics

Require FDA Pre-market Approval

- Regulated as "361 Products"
  - Musculoskeletal tissue
  - Cadaveric cornea
  - Hematopoeitic stem cells if minimally manipulated and intended for homologous use

Do Not Require Pre-market Approval

Principles of Good Product Development

- Drug development should be an orderly process designed to minimize risk and determine benefit to patients
- Clinical studies are required to produce the evidence to determine risks and benefits of the investigational agent
- Clinical development is most effective when there is understanding and communication among sponsors, regulatory authorities and investigators

Safety is Always Primary

- "FDA's primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects, and, in Phase 2 and 3, to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug's effectiveness and safety."

– *IND Regulations [21 CFR 312.22 (a)]*

Clinical Trials - What and Why?

- A prospective study comparing the effects of intervention(s) against a control in human beings."
  - Freeman, Furberg, Demets, 1995

- "The purpose.... is to distinguish the effect of the drug from other influences, such as spontaneous change...placebo effect, or biased observation."
  - 21 CFR 314.126

Clinical Trials

- Assess efficacy by comparing outcomes in groups receiving the drug with controls
- Try to isolate receipt or non-receipt of the drug as the only important difference between groups
- Gold standard is randomized trial where balance is insured by the randomization process
  - May stratify randomization to balance for important prognostic variables

Clinical Trials (cont'd)

- Trials that do not use randomization may have imbalance in important variables (known or unknown)
  - Concurrent controls
  - Historical controls

Clinical Protocol

- Written plan for how the drug/biological agent is to be studied, and the procedures to be followed by each investigator at every clinical site
- Elements
  - objectives
  - background/rationale
  - inclusion and exclusion criteria (eligibility criteria)
  - administration of the test article
  - patient safety and efficacy evaluations – specifics of evaluations, how often and when they will be performed
  - analytical plan (statistical analyses)

Informed Consent

- A sample informed consent document should be submitted with each new study protocol
- It should clearly state the potential risks associated with study participation
- It should not make claims of benefit, overstate potential benefits or minimize potential risks
  - benefit to individual participants vs. societal benefits

Stages of Drug Development

- Phase 1 - first introduction into man
- Phase 2 - hypothesis-generating
- Phase 3 - hypothesis-confirming
  - Large, multicenter
- License application (BLA/NDA)
  - Review... advisory committee (if necessary)... approval
- Phase 4 (Post Marketing Commitments)

Study Objectives: Phase 1

- Usually cohorts of patients exposed to increasing doses of test agent
  - Starting dose - based on animal data, other studies
- Evaluate safety, tolerability, determine Maximum Tolerated Dose (MTD) and any Dose Limiting Toxicities (DLT)
- Identify dose(s) for future studies
- Characterize PK and PD parameters
- Safety in special populations

Study Objectives: Phase 2

- Obtain preliminary evidence that the drug/biologic has an effect
- Includes controlled clinical studies conducted to evaluate:
  - Dose-response
  - "Activity"of the drug/biologic for a particular indication in patients with that disease or condition
  - The common short-term side effects and risks associated with the drug/biologic

Study Objectives: Phase 3

- Confirmation of hypothesis(es) from Phase 2
- Performed after preliminary evidence of safety and effectiveness of the drug/biologic has been obtained
- Intended to gather the substantial evidence of safety and effectiveness needed to evaluate the overall benefit-risk and provide an adequate basis for physician labeling

Studies Should be Adequate and Well-Controlled...

- Design
  - Study population
  - Choice of control
  - Endpoints
- Execution
  - Follow the protocol
- Analysis
  - Accounting of study participants
  - Missing values and how they will be imputed

Guidance for Industry: Providing Evidence of Effectiveness for Human Drug and Biological Products

http://www.fda.gov/cber/guidelines.htm

1962 Drug Amendments to FD&C Act required manufacturers to establish effectiveness by "substantial evidence"

Summary

- Good product development is an orderly process that includes well-designed, well-executed, scientifically valid, interpretable clinical studies
- Goal is to determine the risks and benefits of new therapies, and enable FDA to write practical, unambiguous product labeling for physicians,other healthcare providers and for patients

Summary (cont'd)

- Safety is FDA's primary concern in all phases of clinical development
- The same standards apply to drugs/ biologics for orphan indications as for drugs/biologics intended to treat large patient populations