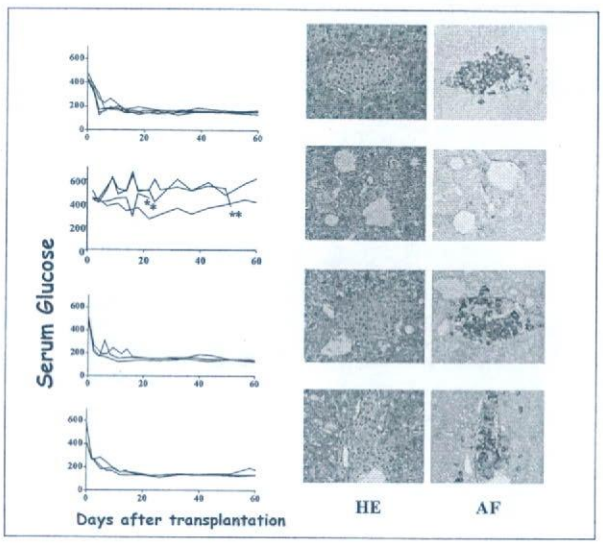
Essential requirement of NKT cells/IFNγ producing cells in early loss of islet grafts

NKTKO/STZ/ 200islets

NKTKO/STZ/ 200isletsWT LMNC

NKTKO/STZ/ 200 islets/ NKT KO LMNC

NKTKO/STZ/ 200 islets/ IFNγ KO LMNC

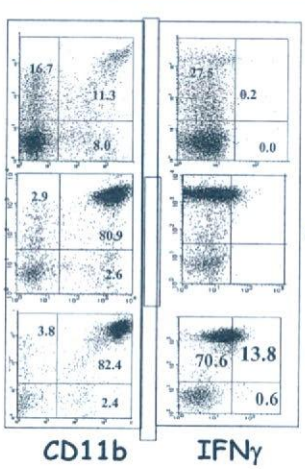


Neutrophil influx and their IFNγ production

Naïve B6

Diabetic NKT-KO/ islets

Diabetic B6/ islets

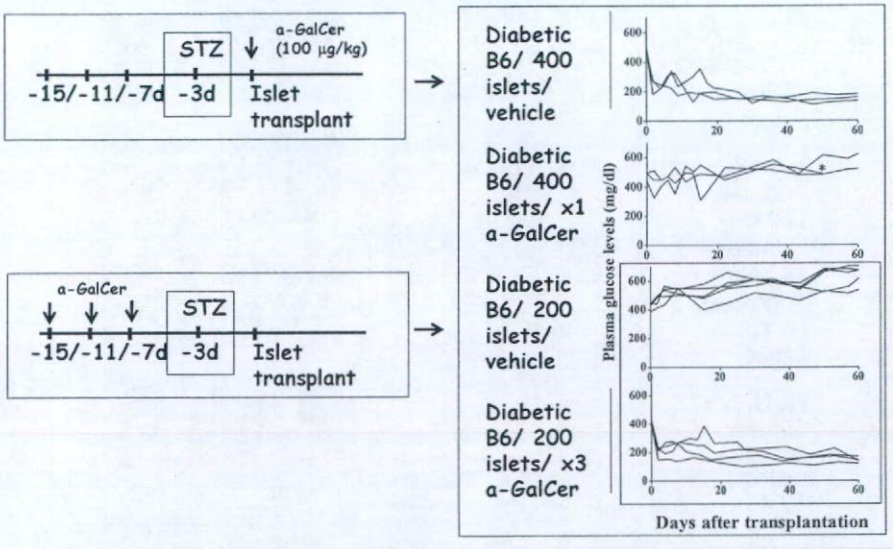


accept

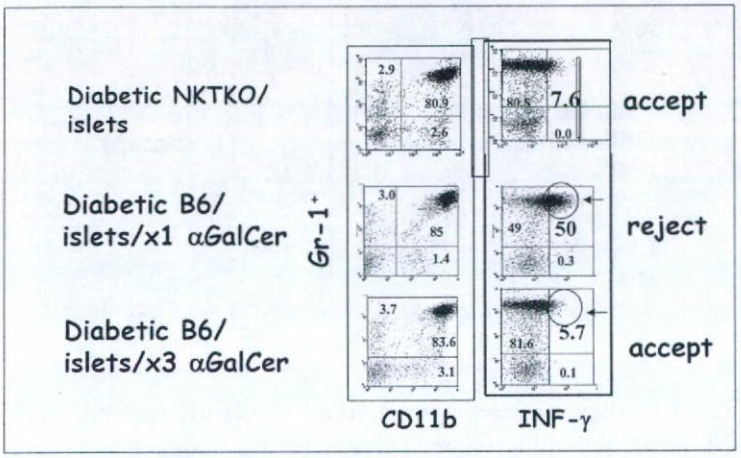
reject

Islet transplantation induces neutrophils without NKT cells
Neutrophil production of IFNγ is NKT cell dependent

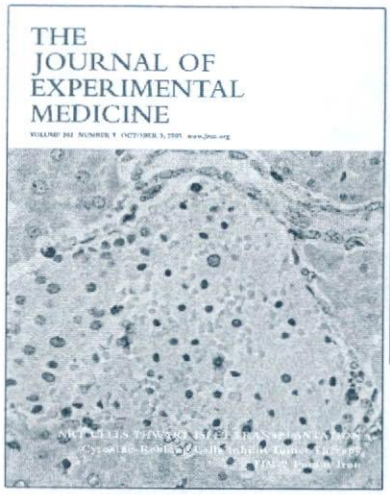
Repeated administrations of α-GalCer down-regulate INF-γ production of NKT cells to prevent early graft loss



Prevention of IFNγ production from Neutrophils by repeated α-GalCer treatment



Vα14 NK T cell–triggered IFN-γ production by Gr-1$^+$CD11b$^+$ cells mediates early graft loss of syngeneic transplanted islets



Nature Rev Immunol 5: 830, 05

Yasunami, et al.
JEM 202: 913, 2005

Our strategy to improve outcome of clinical islet transplantation

is to

find drugs which have already been used in clinical practice and have beneficial effects on prevention of early loss of islet grafts in the liver.

One such candidate includes anti-IL-6R antibody, adenosine, anti-proinflammatory cytokine antibodies, activated protein C, - - - - -.

Anti-IL-6R antibody has been introduced into clinics to treat Castlemann's disease and will be commercially available this year for the treatment of rheumatoid arthritis.

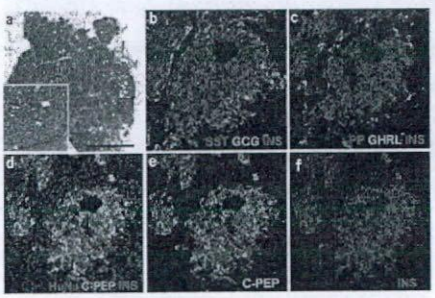
To overcome obstacles facing clinical islet transplantation

#1. Loss of transplanted islets
- → novel procedures for its prevention
  regeneration of transplanted islets
  regeneration of islets in recipient pancreas

#2. limited source of donors
- → xenogeneic (porcine) islets
  ES cells
  iPS cells

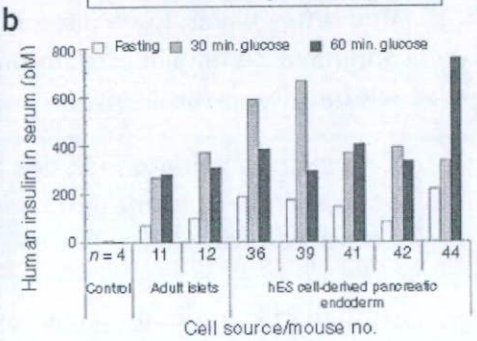
Stage 4 培養ヒトES細胞の移植

Morphology



Retrieved grafts 78d post implant from epididymal fat pads of recipient SCID mice

IPGTT 94 d post implant



Nature Bio Tech on line pub, 2008

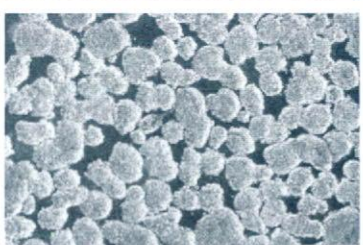
Insulin-producing cells derived from human ES and iPS cells as donors for the treatment of IDDM

#1. tumor formation after purification of pancreatic endoderm? Safety?

#2. control of allo- and auto-immune rejection?

Historical background of islet transplantation

1967	Islet isolation from rat pancreas (Lacy and Kostianovski. Diabetes)
1973	Experimental islet transplantation (Kemp, Scharp, Lacy, Ballinger. Nature)
1982	Islet isolation in large animals ⟶ (P Lacy, E Lacy, Finke, Yasunami. Diabetes)
1986	Mass isolation of human islets (Ricordi, Scharp, Lacy. Diabetes)
1990	First case of clinical islet transplantation (Scharp, Ricordi, Lacy et al. Diabetes)
1991	Foundation of International pancreas & Islet Transplant Association (IPITA) ⟶
2000	Successful islet transplantation (Shapiro, et al. NEJM)
2004	First case of islet transplantation in Kyoto Univ
2006	Islet transplantation in Fukuoka Univ
2007	Suspended due to Liberase problem

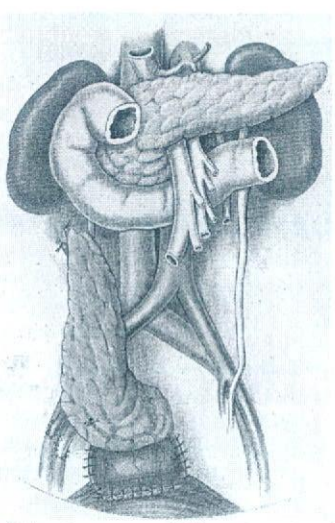


Isolated canine islets

膵島創出に向けた細胞操作技術の開発

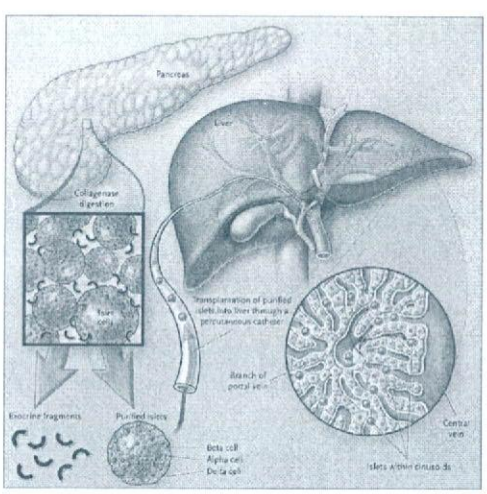
1. 横浜市立大学　大学院医学研究科　臓器再生医学
2. 理化学研究所　発生再生科学総合研究センター
谷口英樹[1, 2]

臓器移植



Atlas of Liver, Pancreas, and Kidney Transplantation

細胞療法

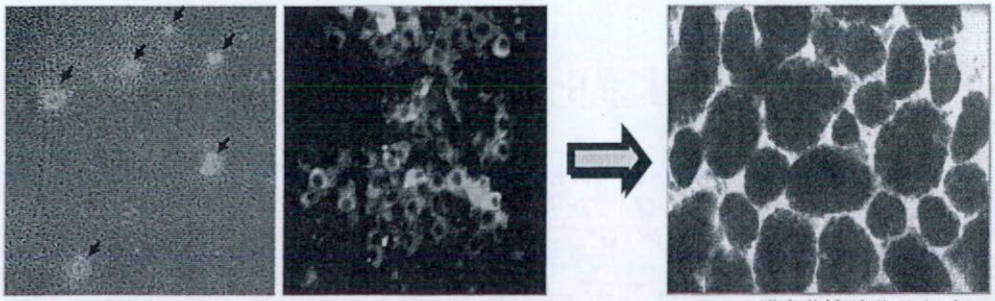


New England Journal of Medicine 350 (7): 694, 2004

細胞操作技術に基づく膵島創出への期待

三次元培養系を活用した膵島再構成への展望

＜膵幹細胞の二次元培養＞　　＜三次元構造を有する膵島＞



膵島移植ガイドラインより

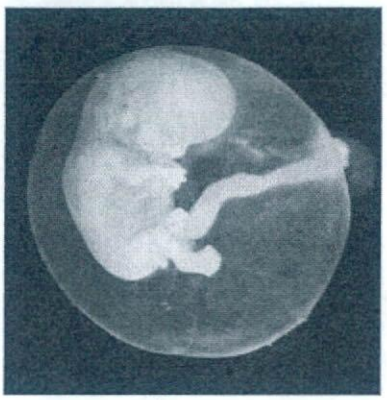
・生体外における膵島スフェロイドの再構成は可能か？
・膵島スフェロイドの大量創出は可能か？
・再構成された膵島の機能は？　その治療効果は？
・膵島スフェロイドの血管化による高度化は可能か？

膵島創出のための要素技術の開発

1. 膵島スフェロイド大量作成技術の開発
2. 膵島スフェロイドの血管化技術の開発

重力分散型模擬微小重力発生装置を活用した3次元大量培養システムの構築

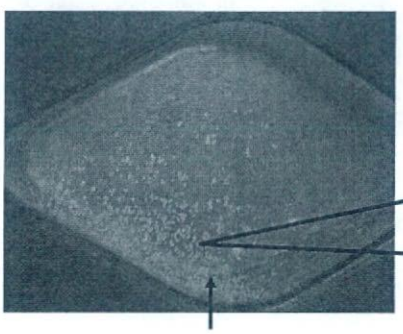
模擬微小重力環境発生装置
2軸回転により重力方向を分散する



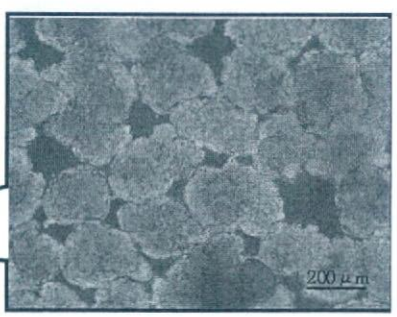
医工連携プロジェクト

模擬微小重力発生装置による膵b細胞株の3次元培養

RIN;2 x 10^5cells/mlにて搭載, 96時間培養後

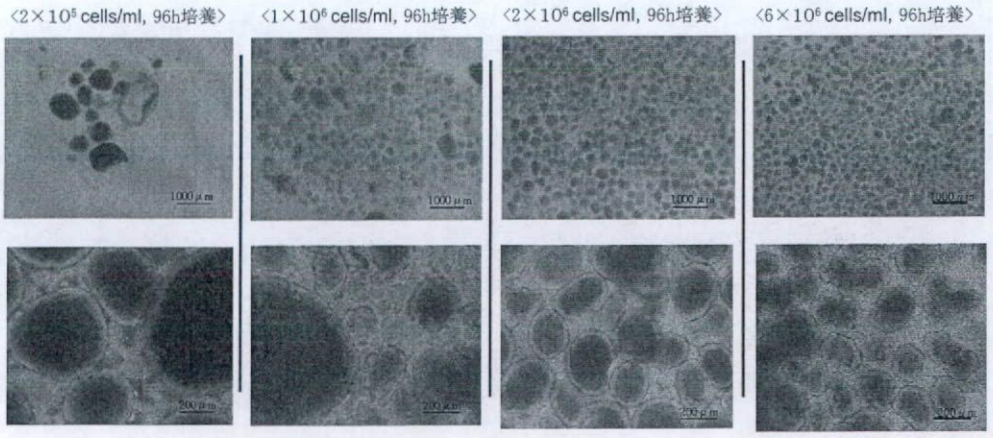


スフェロイド(白色浮遊物)

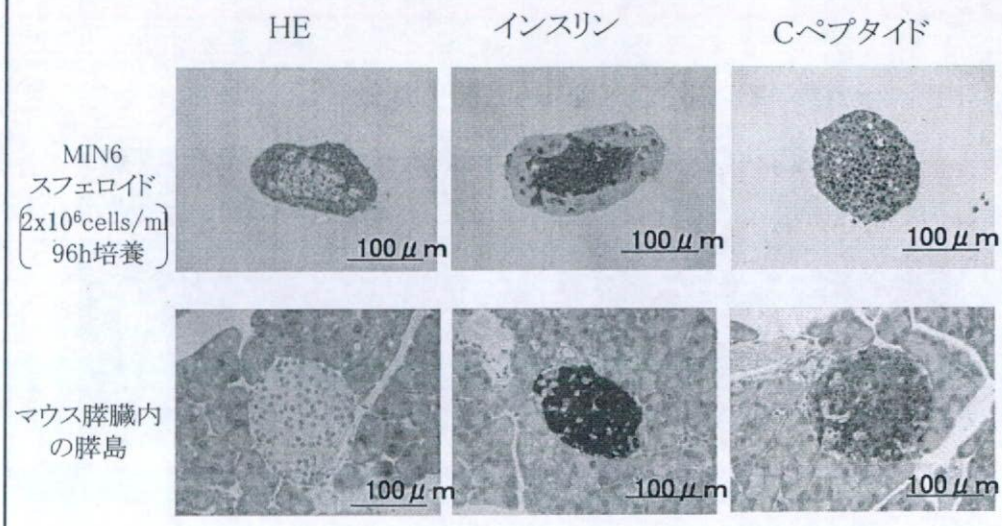


多数のスフェロイドが形成

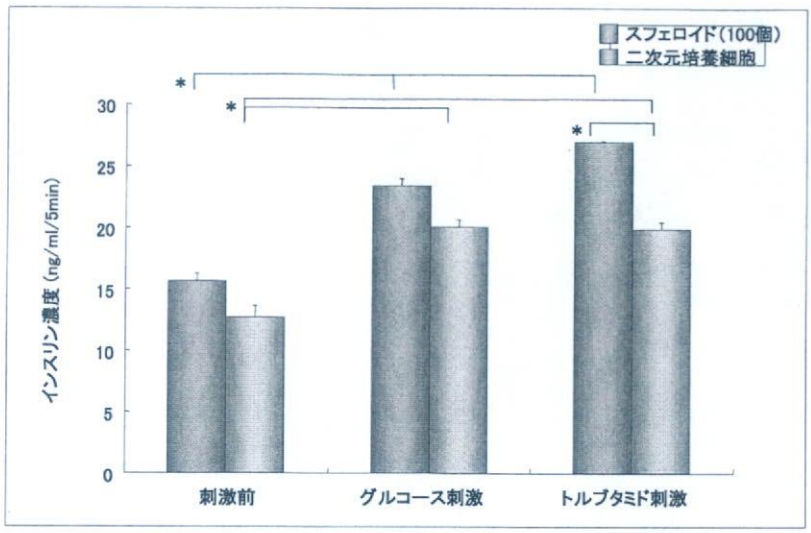
三次元培養によるMIN 6 スフェロイドの大量創出



MIN6スフェロイドにおけるインスリンおよびCペプタイドの産生



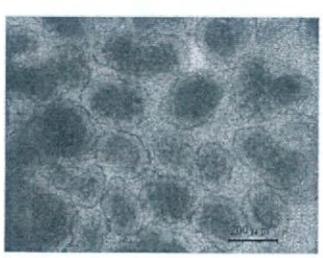
MIN6スフェロイドにおけるグルコース応答性



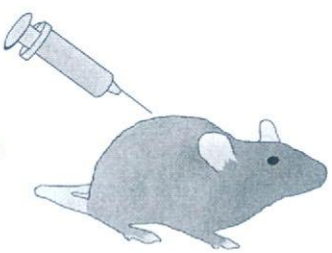
※刺激前:0.5%, グルコース刺激:3%, トルブタミド:1 mM
※総スフェロイド構成生細胞数および二次元培養細胞数は共に8×10^5 cells

糖尿病モデルマウスへの膵島スフェロイドの移植

三次元培養により形成された
MIN6（C57BL/6由来）スフェロイド
（2×１０^{6}cells/ml, 96h培養）



細胞外マトリックスと共に
マウス腎皮膜下に移植
（移植細胞/50μl マトリゲル）



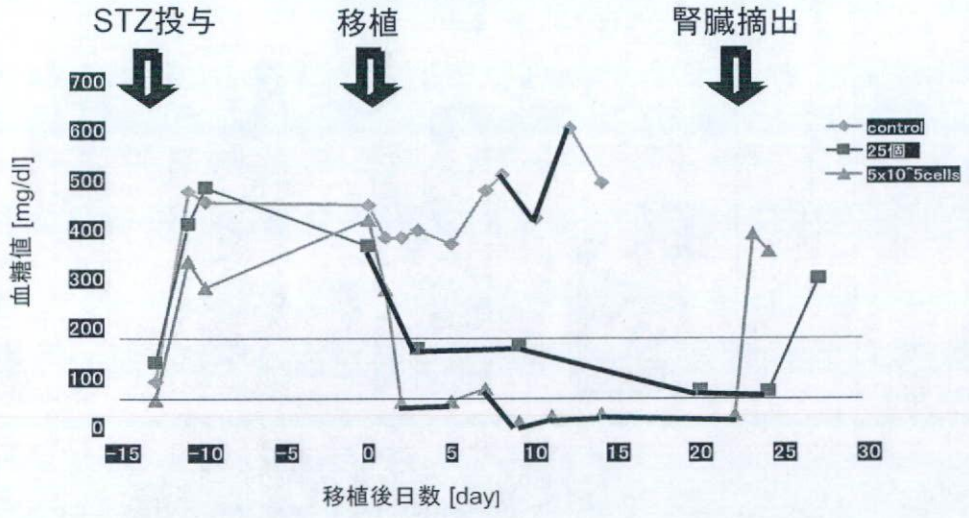
C57BL/6マウス・♂・6週齢
（STZ投与により糖尿病を惹起）

解析方法

・血糖値・体重の経時的測定
・移植組織の組織学的解析
（HE染色、免疫染色）

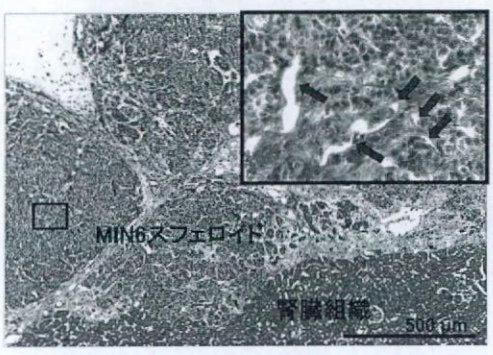
MIN6スフェロイドの移植により糖尿病が改善

空腹時血糖値の推移



糖尿病マウスの腎皮膜下に生着した膵島スフェロイド

MIN6スフェロイド移植



■ DAPI ■ Insulin

スフェロイド内に形成された血管構造

MIN6スフェロイド25個: 5×10^{5}cells

移植後37日目

膵島創出のための要素技術の開発

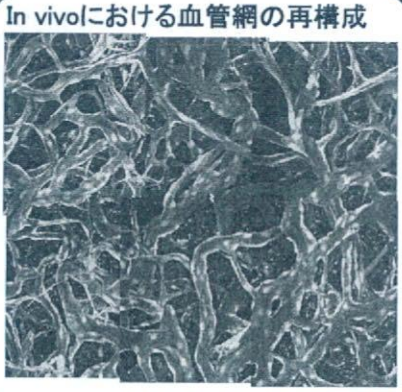
1. 膵島スフェロイド大量作成技術の開発
2. 膵島スフェロイドの血管化技術の開発

膵島スフェロイドにおける血管ネットワークの再構成

膵島スフェロイド内部への血流供給
分泌タンパク質の血流へのアクセス
細胞極性の再構築
↓
膵島スフェロイドの高機能化

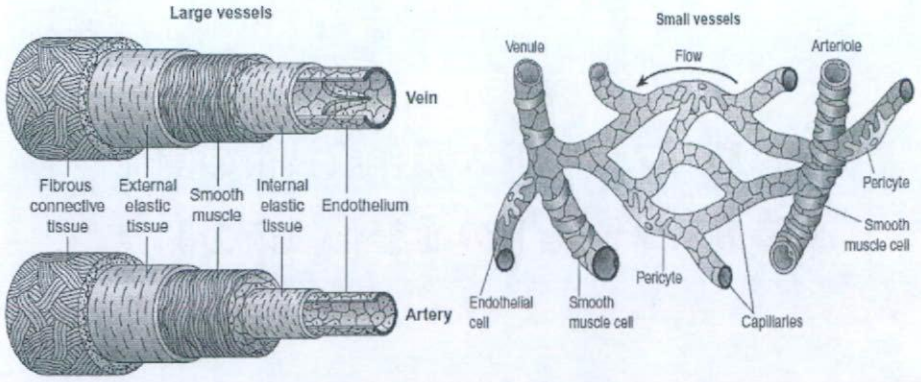
幹細胞ニッチ（vasclar niche）の確保
内部血管をレシピエント型に置換
↓
膵島スフェロイドの長期維持

In vivoにおける血管網の再構成



Koike N, et al: Nature, 2004

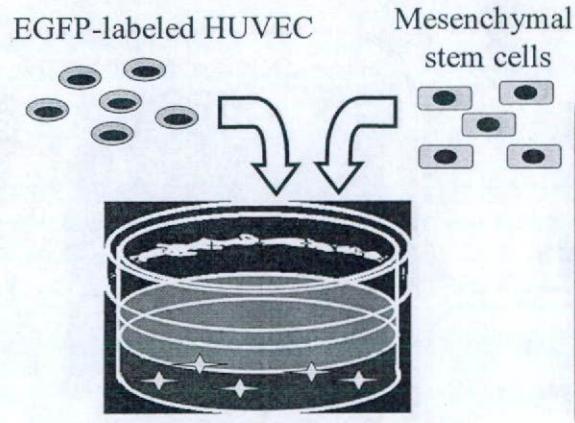
血管の構成細胞



血管内皮細胞 血管の内腔を構成する細胞

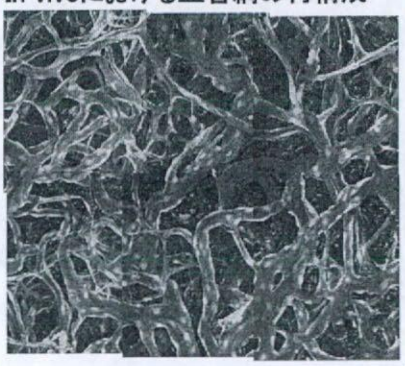
血管壁細胞 毛細血管ではペリサイトとして、動脈・静脈では平滑筋細胞として血管の安定化に寄与する。周囲の間葉系細胞が分化したものである。

生体材料を用いた血管化技術の開発



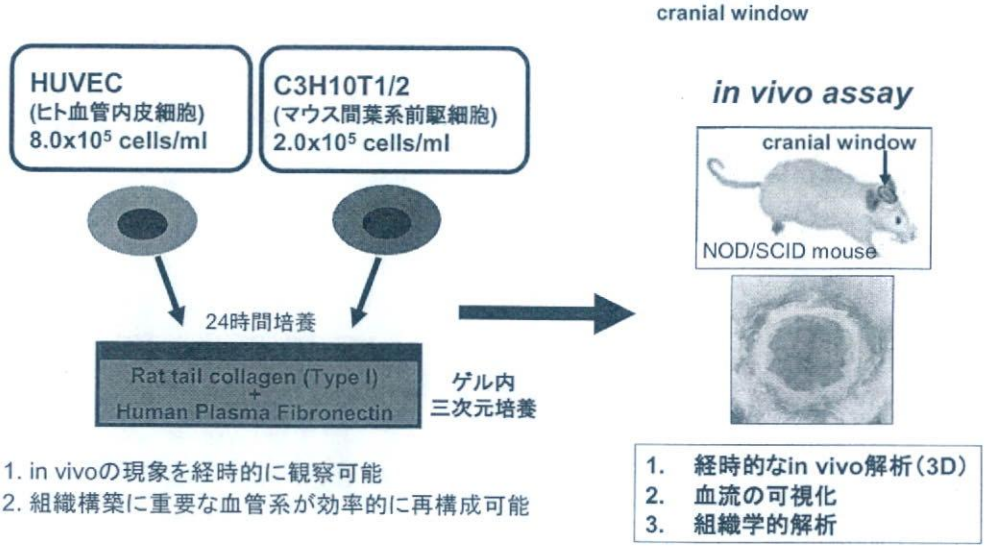
本プロジェクトにて創出される
血管誘導作用を有する新規生体材料

In vivoにおける血管網の再構成



Koike N, et al: Nature, 2004

ヒト/マウスキメラ血管ネットワークの再構成法

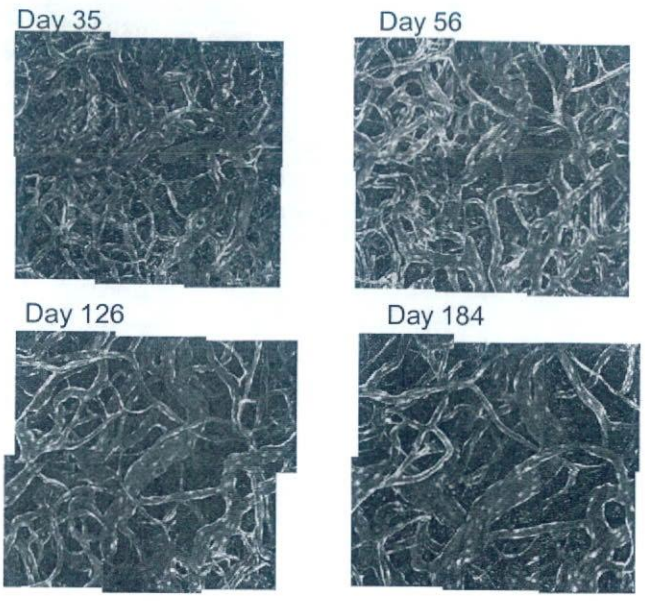


1. in vivoの現象を経時的に観察可能
2. 組織構築に重要な血管系が効率的に再構成可能

1. 経時的なin vivo解析(3D)
2. 血流の可視化
3. 組織学的解析

Koike N. *et al.* ***Nature*** 428, 138-139, 2004

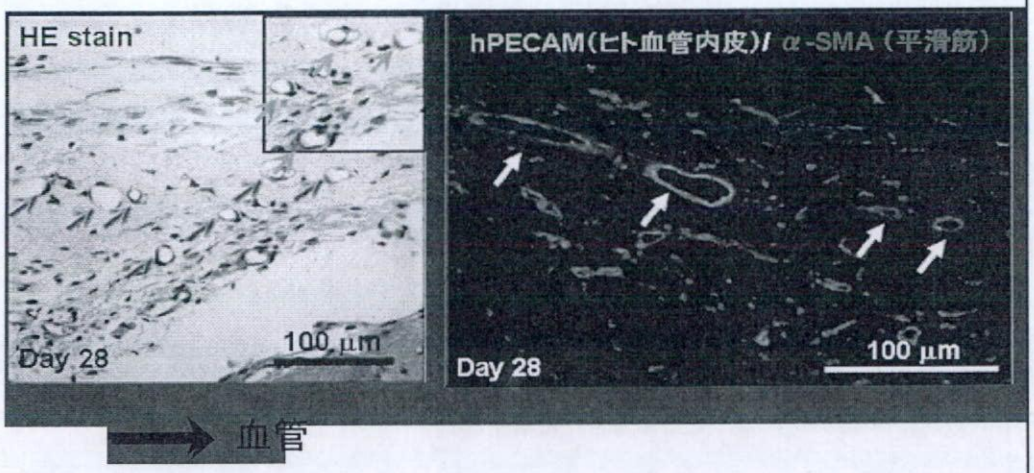
再構成されたヒト/マウスキメラ血管ネットワーク



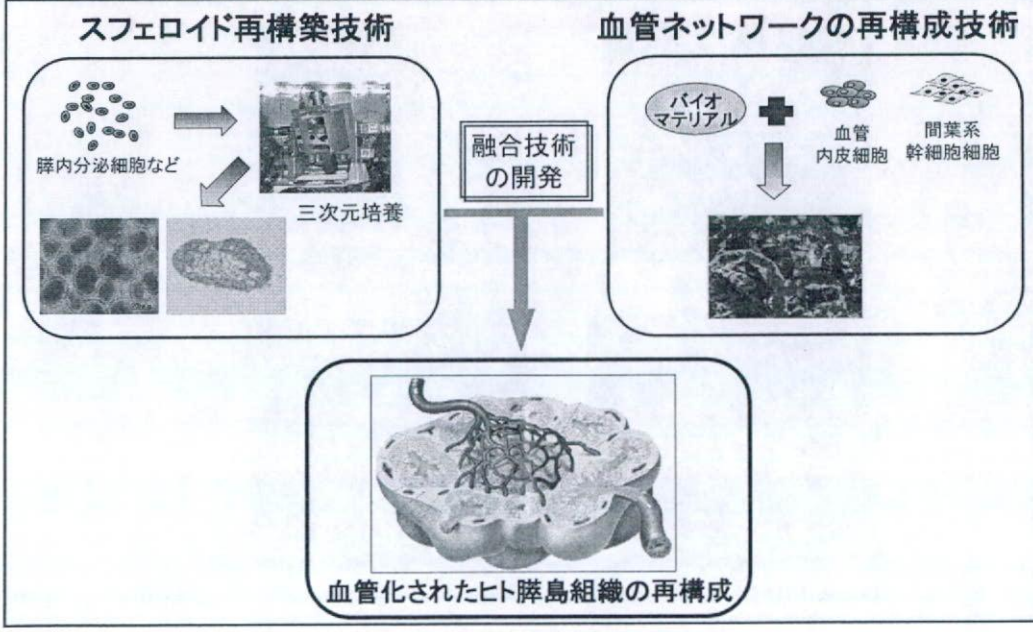
Green:EGFP-HUVEC Red:Rhodamin-Dextran(bloodflow)

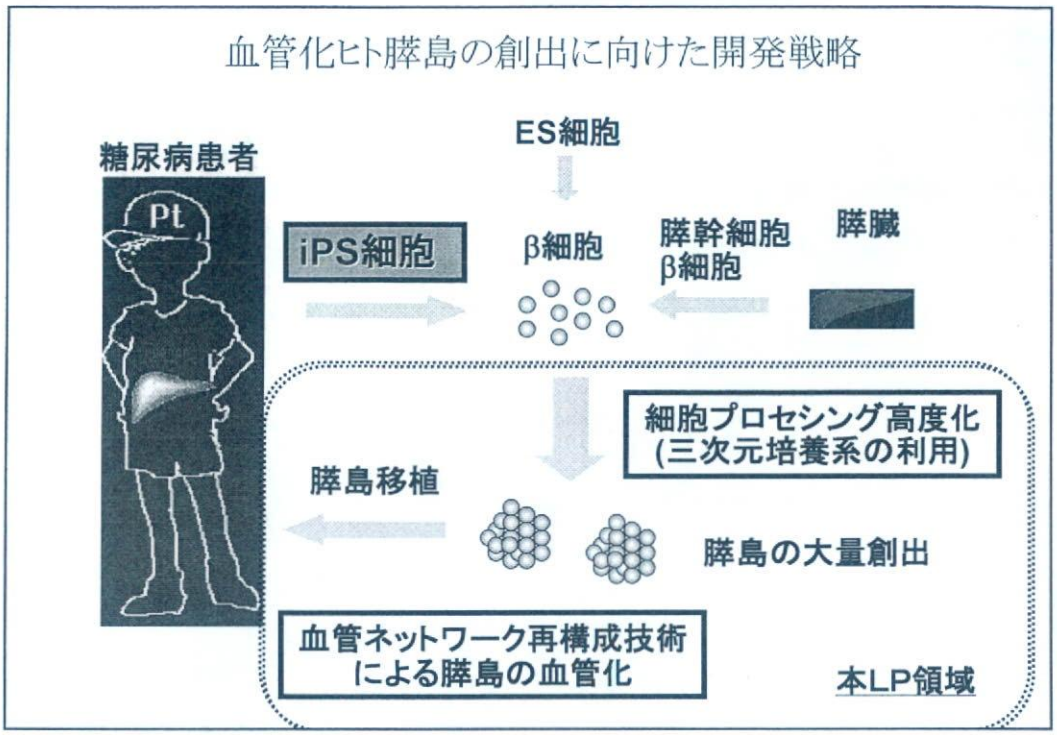
Koike N, *Nature*, 2004

ヒト/マウスキメラ血管ネットワークの組織学的解析



今後の計画　要素技術の融合に基づく高次組織の創出





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膵島細胞の再生

Record 1 of 77
Author(s): Butler, PC (Butler, Peter C.); Meier, JJ (Meier, Juris J.); Butler, AE (Butler, Alexandra E.); Bhushan, A (Bhushan, Anil)
Title: The replication of beta cells in normal physiology, in disease and for therapy
Source: NATURE CLINICAL PRACTICE ENDOCRINOLOGY & METABOLISM, 3 (11): 758-768 NOV 2007
ISSN: 1745-8366

Record 2 of 77
Author(s): Movassat, J (Movassat, J.); Calderari, S (Calderari, S.); Fernandez, E (Fernandez, E.); Martin, MA (Martin, M. A.); Escriva, F (Escriva, F.) ; Plachot, C (Plachot, C.); Gangnerau, MN (Gangnerau, M. N.); Serradas, P (Serradas, P.); Alvarez, C (Alvarez, C.); Portha, B (Portha, B.)
Title: Type 2 diabetes - a matter of failing beta-cell neogenesis? Clues from the GK rat model
Source: DIABETES OBESITY & METABOLISM, 9: 187-195 Suppl. 2 NOV 2007
ISSN: 1462-8902

Record 3 of 77
Author(s): Butler, AE (Butler, A. E.); Galasso, R (Galasso, R.); Meier, JJ (Meier, J. J.); Basu, R (Basu, R.); Rizza, RA (Rizza, R. A.); Butler, PC (Butler, P. C.)
Title: Modestly increased beta cell apoptosis but no increased beta cell replication in recent-onset type 1 diabetic patients who died of diabetic ketoacidosis
Source: DIABETOLOGIA, 50 (11): 2323-2331 NOV 2007
ISSN: 0012-186X

Record 4 of 77
Author(s): Huang, CJ (Huang, Chang-jiang); Lin, CY (Lin, Chia-yu); Haataja, L (Haataja, Leena); Gurlo, T (Gurlo, Tatyana); Butler, AE (Butler, Alexandra E.); Rizza, RA (Rizza, Robert A.); Butler, PC (Butler, Peter C.)
Title: High expression rates of human islet amyloid polypeptide induce endoplasmic reticulum stress-mediated beta-cell apoptosis, a characteristic of humans with type 2 but not type 1 diabetes
Source: DIABETES, 56 (8): 2016-2027 AUG 2007
ISSN: 0012-1797

Record 5 of 77
Author(s): Langley, AK (Langley, Alissa K.); Suffoletta, TJ (Suffoletta, Terri J.); Jennings, HR (Jennings, Heath R.)
Title: Dipeptidyl peptidase IV inhibitors and the incretin system in type 2 diabetes mellitus
Source: PHARMACOTHERAPY, 27 (8): 1163-1180 AUG 2007
ISSN: 0277-0008

Record 6 of 77
Author(s): Muraca, M (Muraca, M.); Galbiati, G (Galbiati, G.); Realdi, G (Realdi, G.); Vilei, MT (Vilei, M. T.); Fabricio, ASC (Fabricio, A. Sueli Coelho); Caruso, M (Caruso, M.)
Title: Regenerative medicine: An insight
Source: TRANSPLANTATION PROCEEDINGS, 39 (6): 1995-1998 JUL-AUG 2007
ISSN: 0041-1345

Record 7 of 77
Author(s): Greer, RM (Greer, Ristan M.); Shah, J (Shah, Janaki); Jeske, YW (Jeske, Yvette W.); Brown, D (Brown, David); Walker, RM (Walker, Rosslyn M.); Cowley, D (Cowley, David); Bowling, FG (Bowling, Francis G.); Liaskou, D (Liaskou, Daphne); Harris, M (Harris, Mark); Thomsett,MJ (Thomsett, Michael J.); Choong, C (Choong, Catherine); Bell, JR (Bell, John R.); Jack, MM (Jack, Michelle M.); Cotterill, AM (Cotterill, Andrew M.)
Title: Genotype-phenotype associations in patients with severe hyperinsulinism of infancy
Source: PEDIATRIC AND DEVELOPMENTAL PATHOLOGY, 10 (1): 25-34 JAN-FEB 2007
ISSN: 1093-5266

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Author(s): Butler, AE (Butler, Alexandra E.); Huang, A (Huang, Andrew); Rao, PN (Rao, P. Nagesh); Bhushan, A (Bhushan, Anil); Hogan, WJ (Hogan, William J.); Rizza, RA (Rizza, Robert A.); Butler, PC (Butler, Peter C.)
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