生醫工程概論

Tissue Engineering

11/20/2006

Cellular Therapies

- The use of grafted or transfused primary human cells into a patient to affect a pathological condition

TABLE 12.1 Incidence of Organ and Tissue Deficiencies, or the Number of Surgical Procedures Related to These Deficiencies in the United States[a]

Indicator	Procedure or Patients per Year
Skin	
Burns[b]	2,150,000
Pressure sores	150,000
Venous stasis ulcers	500,000
Diabetic ulcers	600,000
Neuromuscular disorders	200,000
Spinal cord and nerves	40,000
Bone	
Joint replacement	558,200
Bone graft	275,000
Internal fixation	480,000
Facial reconstruction	30,000
Cartilage	
Patella resurfacing	216,000
Chondromalacia patellae	103,400
Meniscal repair	250,000
Arthritis (knee)	149,900
Arthritis (hip)	219,300
Fingers and small joints	179,000
Osteochondritis dissecans	14,500
Tendon repair	33,000
Ligament repair	90,000
Blood Vessels	
Heart	754,000
Large and small vessels	606,000
Liver	
Metabolic disorders	5,000
Liver cirrhosis	175,000
Liver cancer	25,000
Pancreas (diabetes)	728,000
Intestine	100,000
Kidney	600,000
Bladder	57,200
Ureter	30,000
Urethra	51,900
Hernia	290,000
Breast	261,000
Blood Transfusions	18,000,000
Dental	10,000,000

[a] From Langer and Vacanti (1993).
[b] Approximately 150,000 of these individuals are hospitalized and 10,000 die annually.

poreal support devices, β-islet cells for diabetes, skin for ulcers and burns, and genetically modified myocytes for treatment of muscular dystrophy. The challenges faced with each tissue are different. A few examples are provided for illustrative purposes.

Key Cellular Fate Processes

- Cell differentiation
- Cell division (mitosis)
- Cell migration (motion)
- Cell death (apoptosis)

Cellular Communication

- Soluble signals
- Direct cell-cell contact
- The extracellular matrix (ECM)

Challenges Facing the Tissue Engineer

- The reconstitution of physical (mass transfer) and biological (soluble and insoluble signals) microenvironments for the development of tissue function
- To overcome scale-up problems in order to generate cellular microenvironments that are clinically meaningful
- The system automation to perform on clinically meaningful scales
- The implementation of devices in clinical settings, with cell handling and preservation procedures that are required for cell therapies

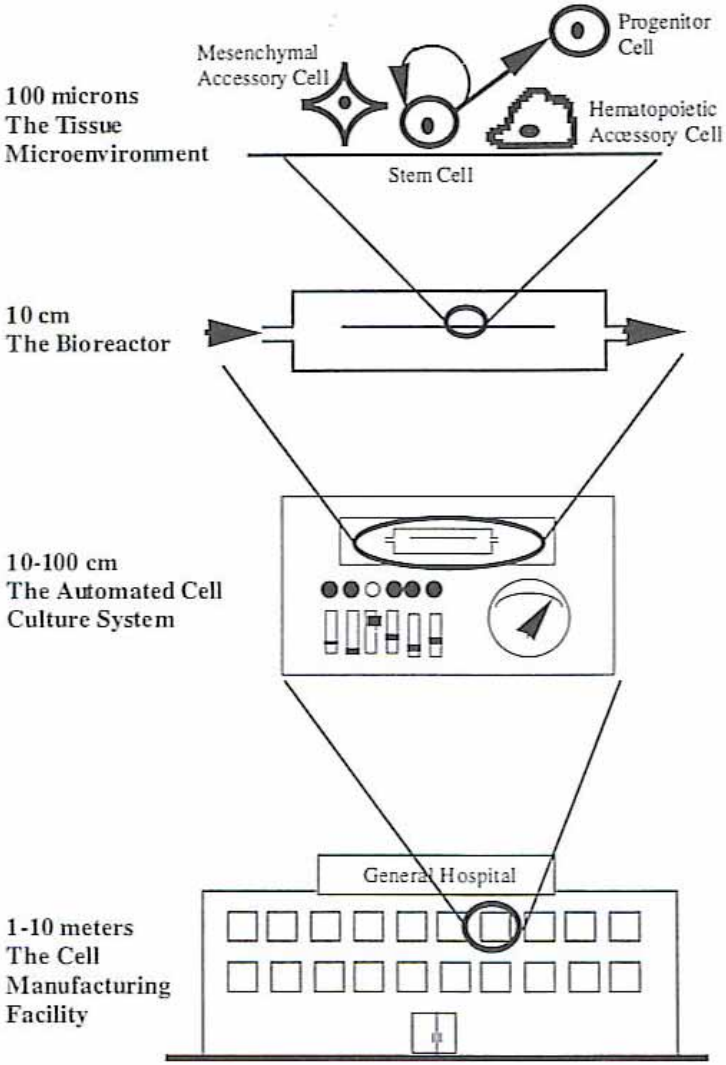


Fig. 12.11 The four principal size scales in tissue engineering and cellular therapies.

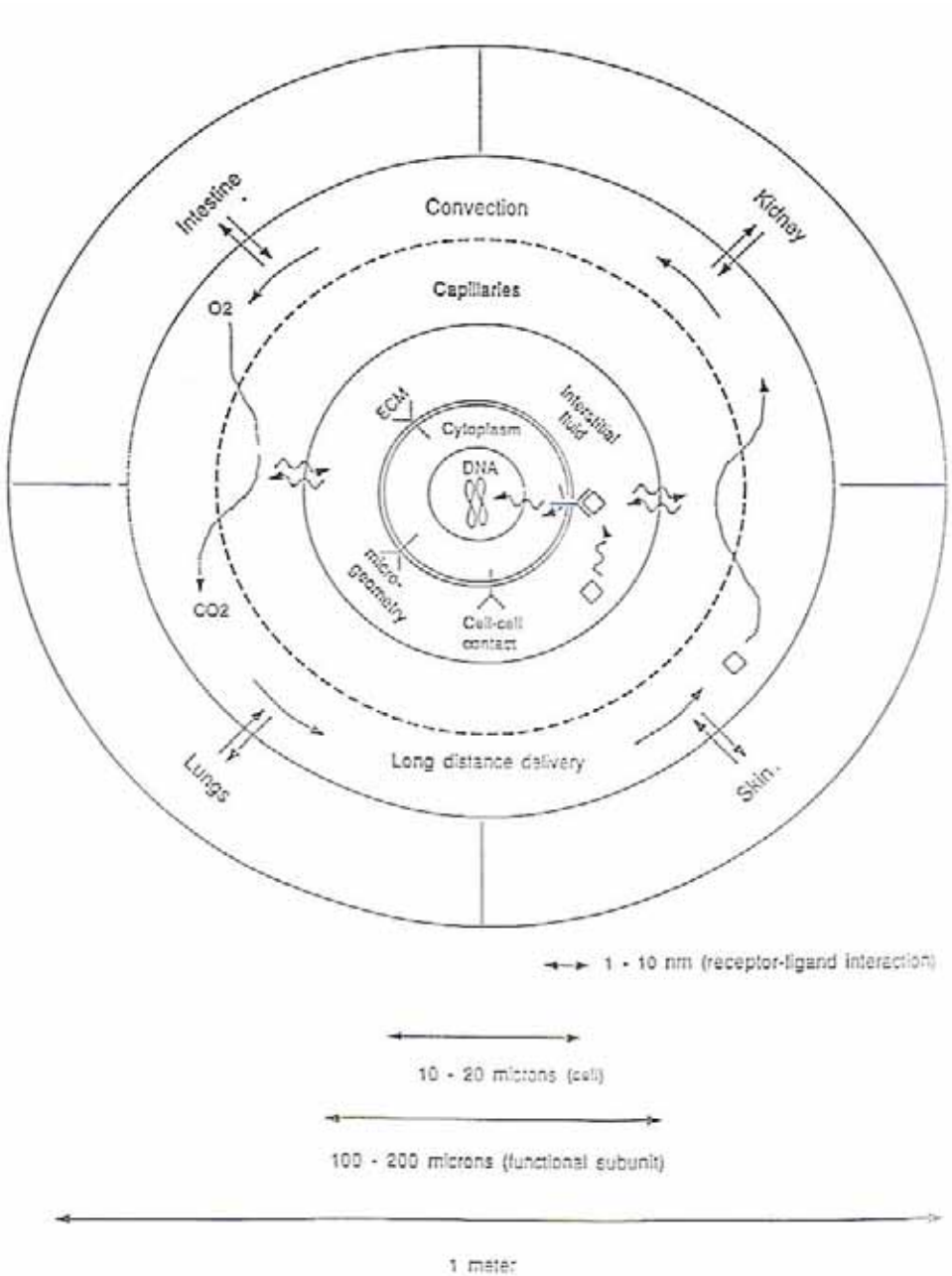


Fig. 12.12 A cell and its communication with other body parts (modified from Lightfoot, 1974).

Human Cells as Therapeutic Agents

- Bone marrow transplantation
- Skin
- Pancreas/β-islet cells
- Cartilage and chondrocytes

Bone Marrow Transplantation

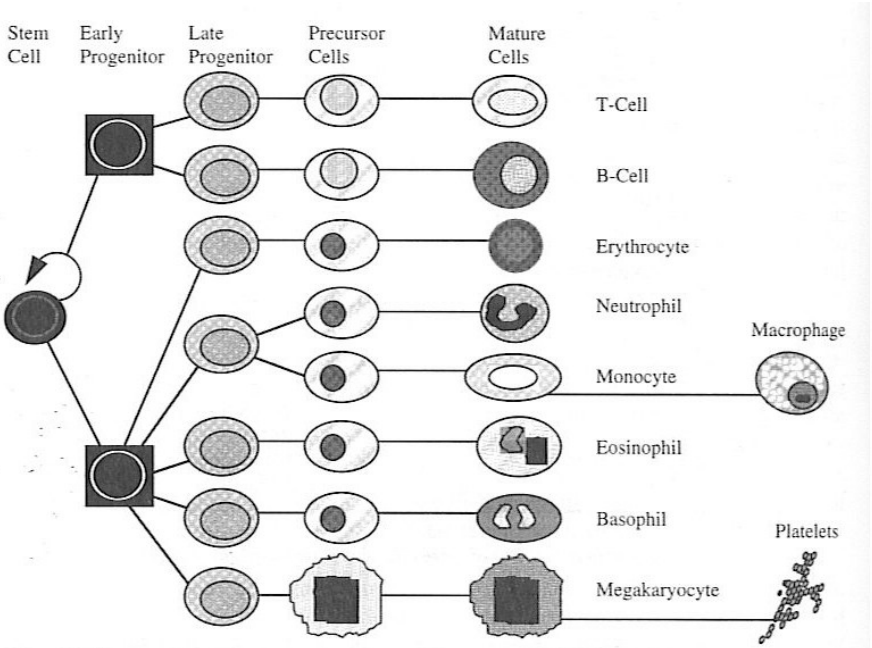


Fig. 12.1 Hematopoietic cell production. The production fluxes through the lineages can be estimated based on the known steady-state concentration of cells in circulation, the total volume of blood, and the half-lives of the cells. Note that the 400 billion cells produced per day arise from a small number of stem cells (from Koller and Palsson 1993).

Bone marrow is composed of 500-1000 billion cells and produces approx. 400 billion myeloid cells daily

Bone Marrow Transplantation

- Autologous transplants
- Allogeneic transplants

Skin

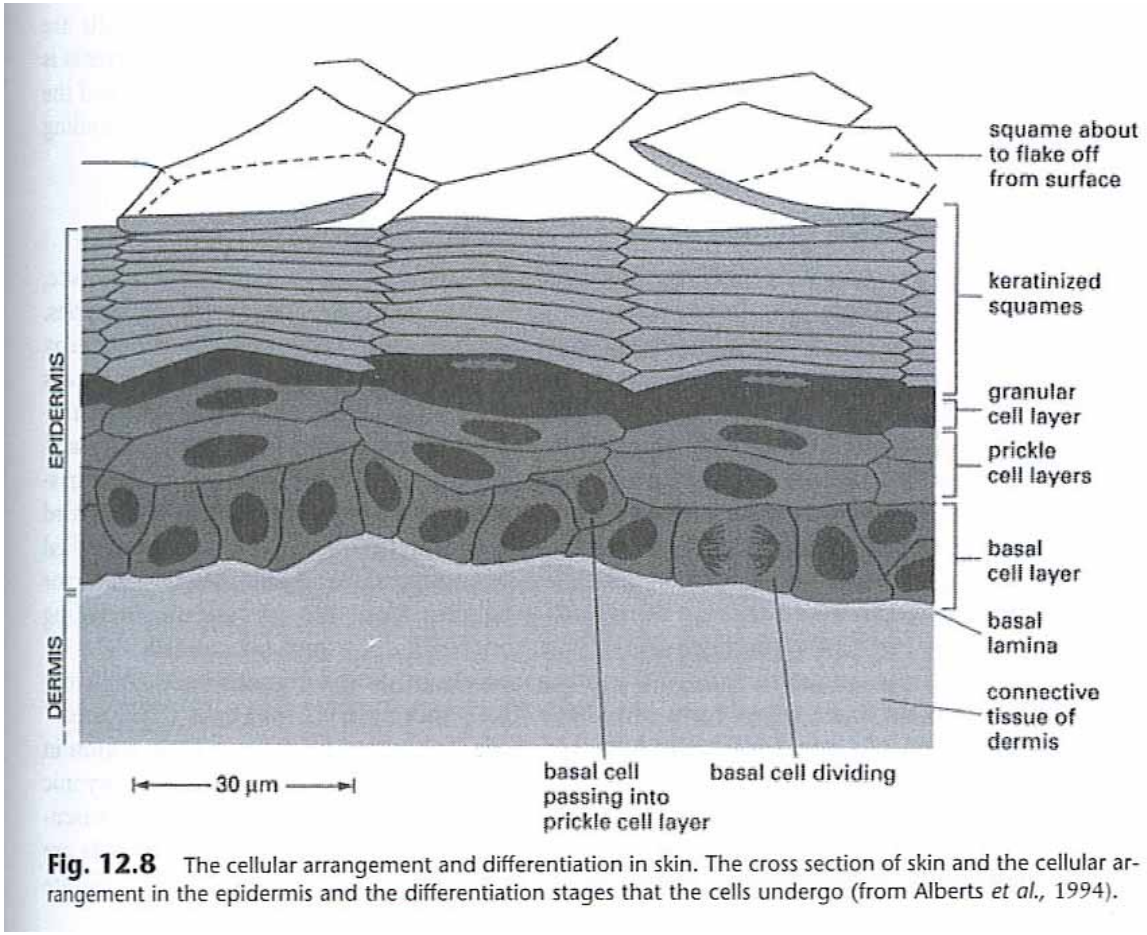


Fig. 12.8 The cellular arrangement and differentiation in skin. The cross section of skin and the cellular arrangement in the epidermis and the differentiation stages that the cells undergo (from Alberts *et al.*, 1994).

Cultured Skin

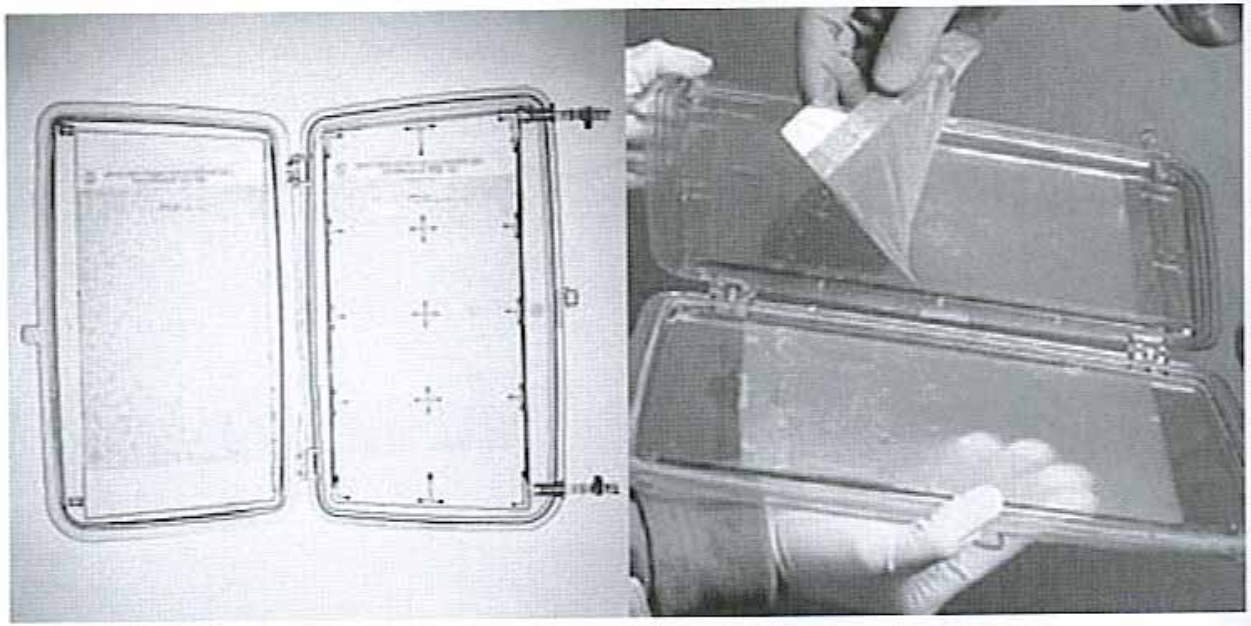


Figure 7.5 Advanced Tissue Sciences bioreactor for culture of their skin product, Trancyte®, derived from human foreskins.

Pancreas and β-islet Cells

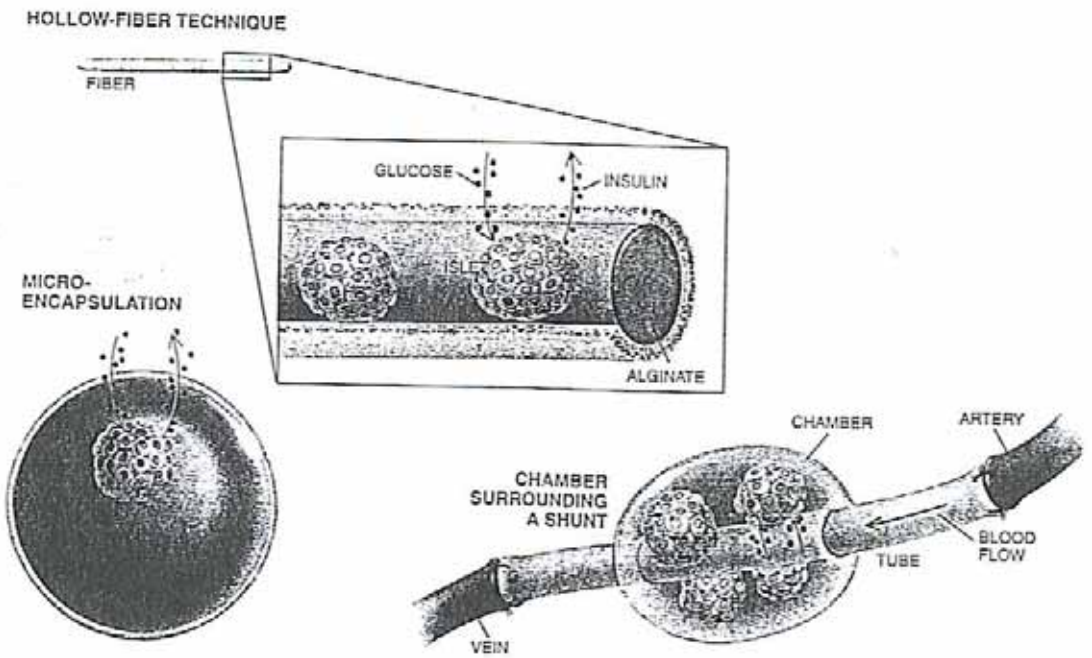


Fig. 12.2 Encapsulation of islets in semiporous plastic is one promising way to protect them from attack by the immune system (from Lacey, 1995).

Cartilage and Chondrocytes

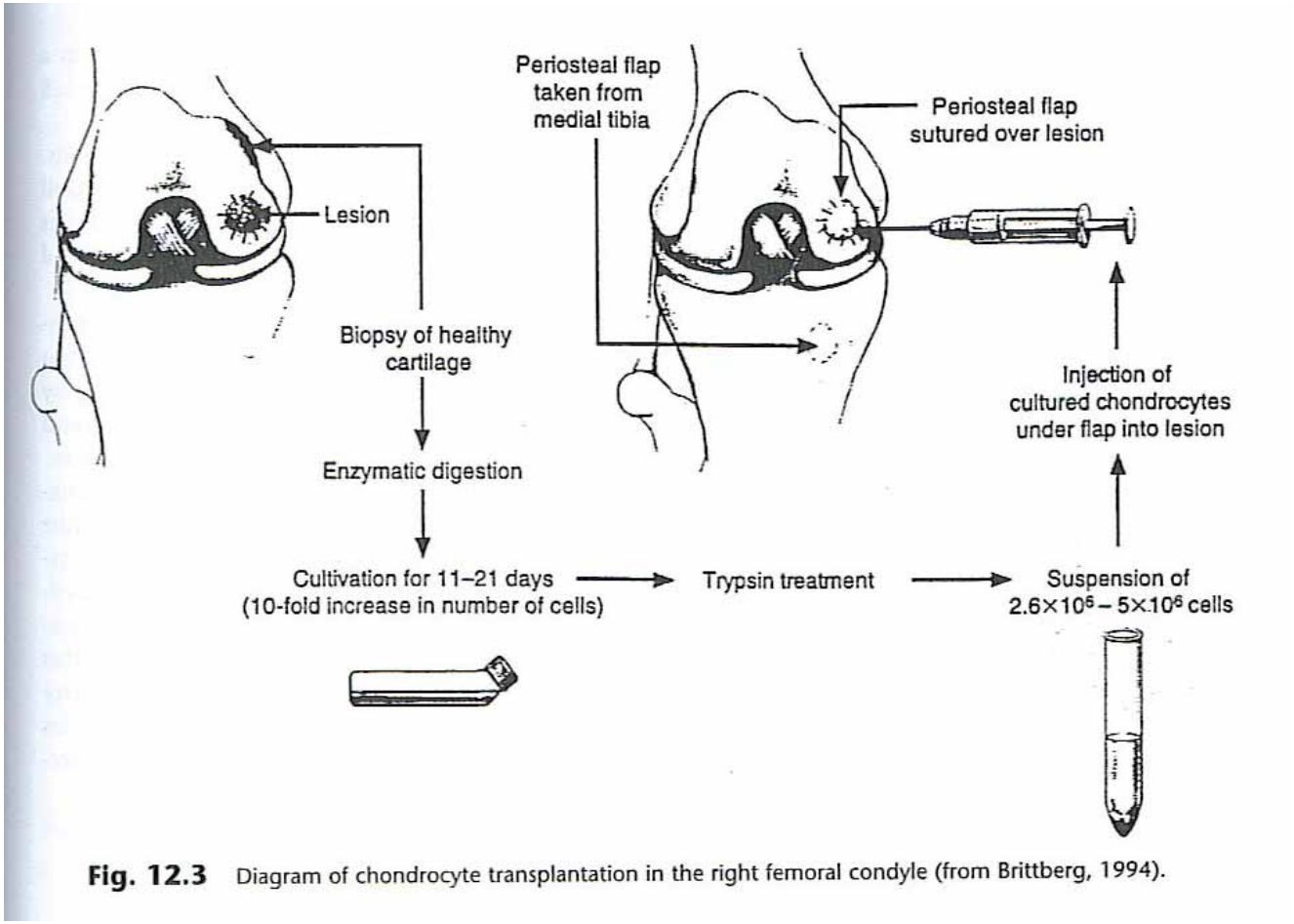


Fig. 12.3 Diagram of chondrocyte transplantation in the right femoral condyle (from Brittberg, 1994).

Fundamental Questions Influence Cell Transplantation

- What are clinically meaningful numbers of cells?
  - Require densities higher than 10 million cells per milliliter
- What are the fundamental limitations to the production of primary cells?
  - Primary human cells can undergo about 30-50 doublings in culture
- How rapidly do primary cells grow in culture?
  - Hematopoietic progenitor cells have 11-12 h doubling time
  - Adult chondrocytes have 24-48 h doubling time

- How are these cells currently produced?
  - T cells (in bags)
  - Chondrocytes (tissue culture flasks)

Cell Numbers *in Vivo*

TABLE 12.2 Cell Numbers in Tissue Biology and Tissue Engineering: Orders of Magnitude

Cell numbers *in vivo*	
Whole body	10^{14}
Human organ	10^{9}–10^{11}
Functional subunit	10^{2}–10^{3}
Cell production *in vivo*	
Theoretical maximum from a single cell (Hayflick limit)	$2^{30-50} < 10^{15}$
Myeloid blood cells produced over a lifetime	10^{16}
Small intestine epithelial cells produced over a lifetime	5×10^{14}
Cell production *ex vivo*	
Requirements for a typical cellular therapy	10^{7}–10^{9}
Expansion potential[a] of human tissues	
Hematopoietic cells	
Mononuclear cells	10-fold
CD34 enriched	100-fold
Two or three antigen enrichment	10^{6}- to 10^{7}-fold
T cells	10^{3}- to 10^{4}-fold
Chondrocytes	10- to 20-fold
Muscle, dermal fibroblasts	$>10^{6}$-fold

[a] Expansion potential refers to the number of cells that can be generated from a single cell in culture.

Factors to Reconstitute Tissue Function

- The nature of the tissue microenvironment
- The dynamics of the cellular communication and metabolic processes

Considerations for Microenvironments

- The design of cell culture devices must produce uniformity in supporting factors such as nutrient, oxygen, growth factor/hormone concentrations
- The above input applications must be reasonably homogeneous down to 100 um distances

Three Dynamic States of Tissues

- Tissue function: the normal steady-state function of tissue
- Tissue formation: the formation of tissue is the field of developmental biology
- Tissue repair: wounded tissue displays a healing process that may be of concern in cell therapies and tissue engineering

Tissue Dynamics

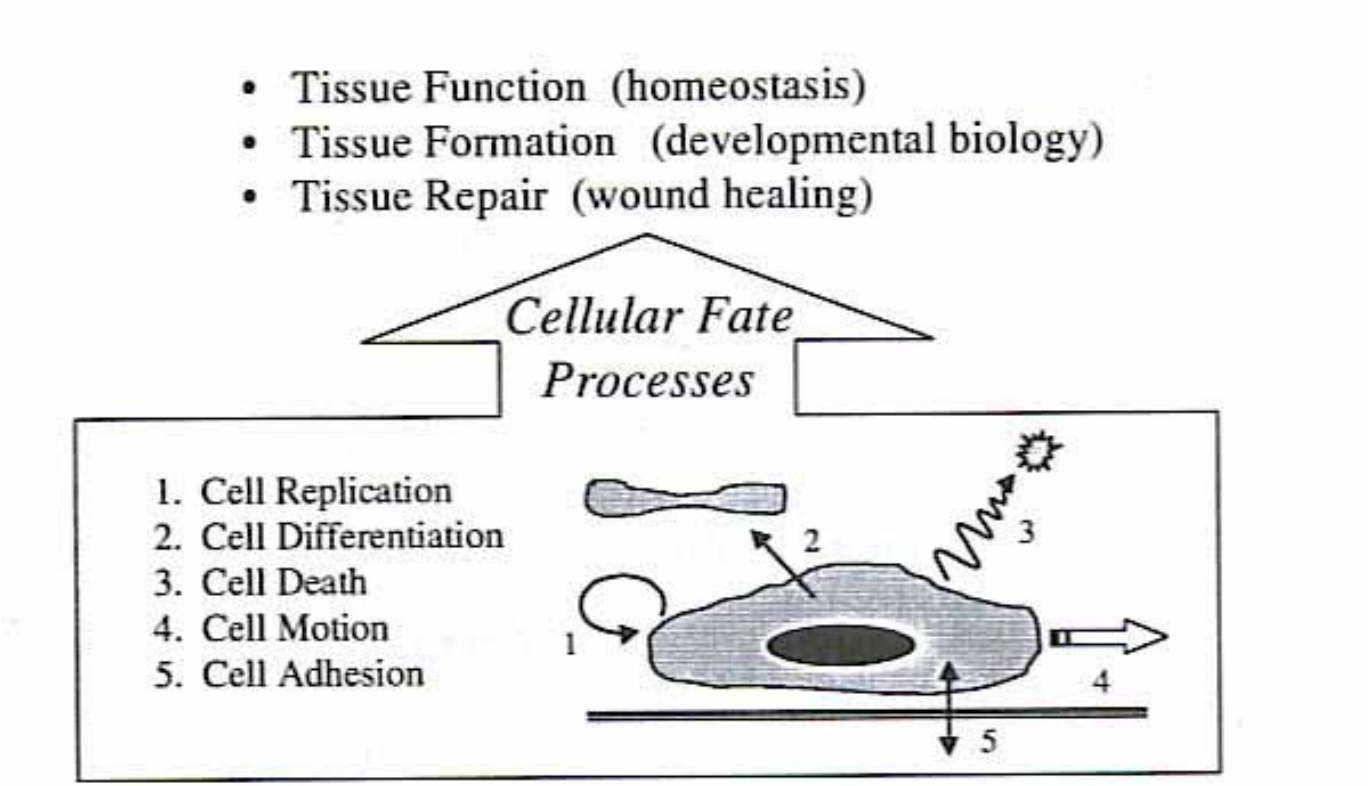
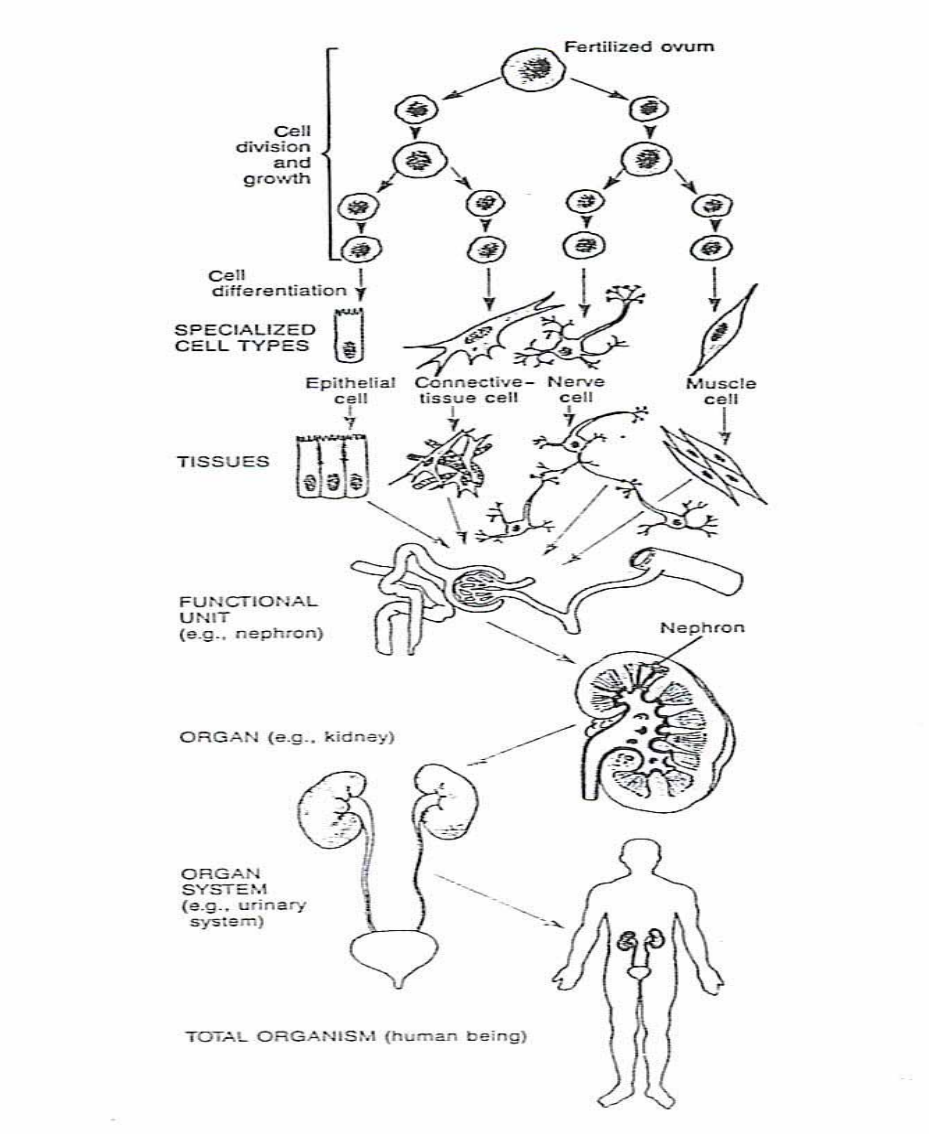


Fig. 12.5 Tissue dynamics. The three dynamic states of tissues and the underlying cellular fate processes.

Tissue Histogenesis



Cellular Fate Processes

- Cell replication - an increase in cell number
- Cell differentiation - changes in gene expression and the acquisition of a particular function
- Cell Motility - the motion of a cell into a particular niche or location
- Cell apoptosis - the controlled death of a cell, distinguished from necrotic death
- Cell adhesion - the physical binding of a cell to its immediate environment, which may be a neighboring cell, extracellular matrix, or an artificial surface

TABLE 12.3 Cell Renewal Rates in Tissues

Tissue	Species	Turnover Time (days)
Erythropoiesis	Rat	2.5
Myelopoiesis	Rat	1.4
Hematopoiesis	Human	2.5
Small intestinal epithelium	Human	4–6
	Rat	1–2
Epidermis	Human	7–100
Coreneal epithelium	Human	7
Lymphatic cells	Rat (thymus)	7
	Rat (spleen)	15
Epithelial cells	Rat (vagina)	3.9
	Human (cervix)	5.7
Spermatogonia	Human	74
Renal interstitial cells	Mouse	165
Hepatic cells	Rat	400–500

Highly Prolific Tissues

- Bone barrow and blood cell formation
- The villi in the small intestine
- Skin

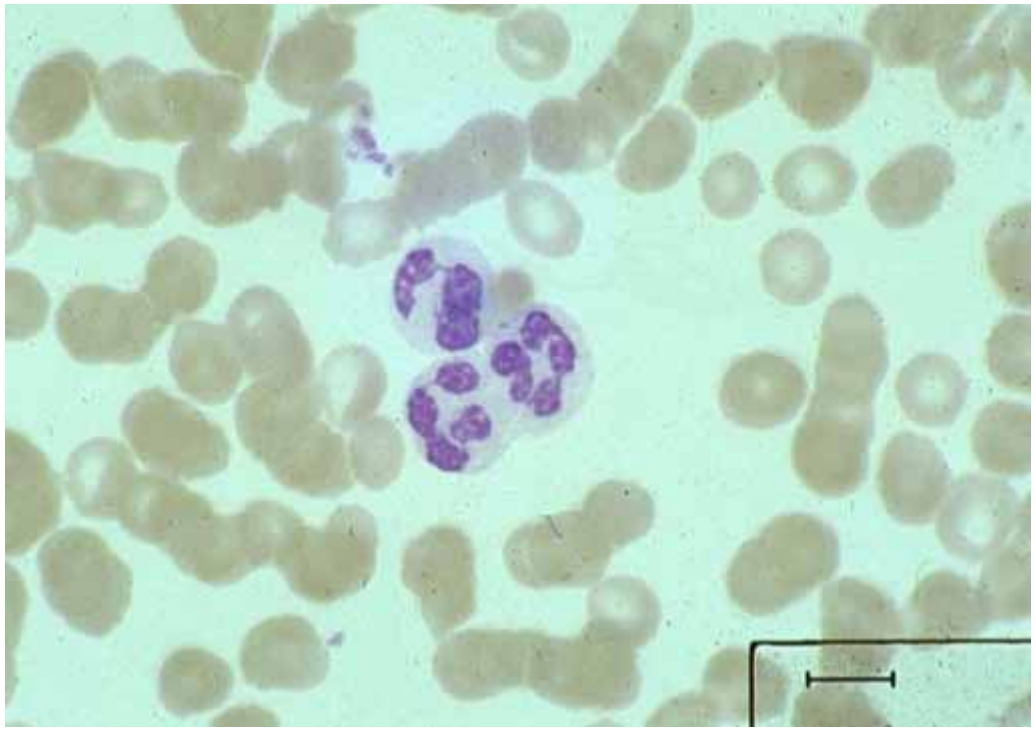
Model for Cell Production in Hematopoiesis

	Stem Cell	Early Progenitor	Late Progenitor	Precursor Cell	Mature Cell
Cell Number	Potential 2^{30}-2^{50} per cell				Need About 10^{16} total over lifetime
Cell Cycling	Very slow (t_d ~ 1/6wks.)	Slow (t_d~60-100hrs.)	Very rapid (t_d ~ 12 hrs.)	Slow	Zero (can be activated in special cases)
Apoptosis	Inactive	Inactive	Very Active (1:5000 survives)	Slow	Inactive (can be induced)
Motility	Zero (except during homing)	Zero	Low	Higher	Function of Physiological State
Regulation	Cell-Cell Contact	Cell-Cell Contact	Soluble Growth Factors	Soluble Growth Factors	Soluble Growth Factors

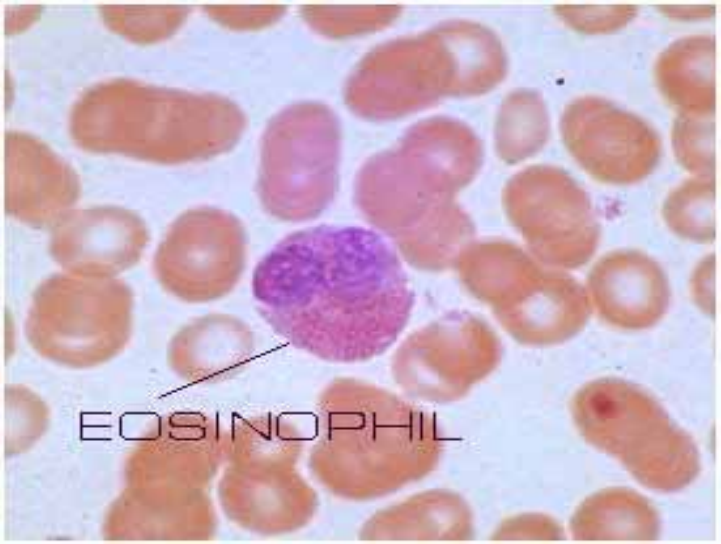
Fig. 12.6 Model for cell production in prolific tissues. This model was derived from decades-long research in hematology. The columns represents increasingly differentiated cells, and the rows indicate the cellular fate processes and other events that cells undergo at different states of differentiation (t_d denotes doubling time).

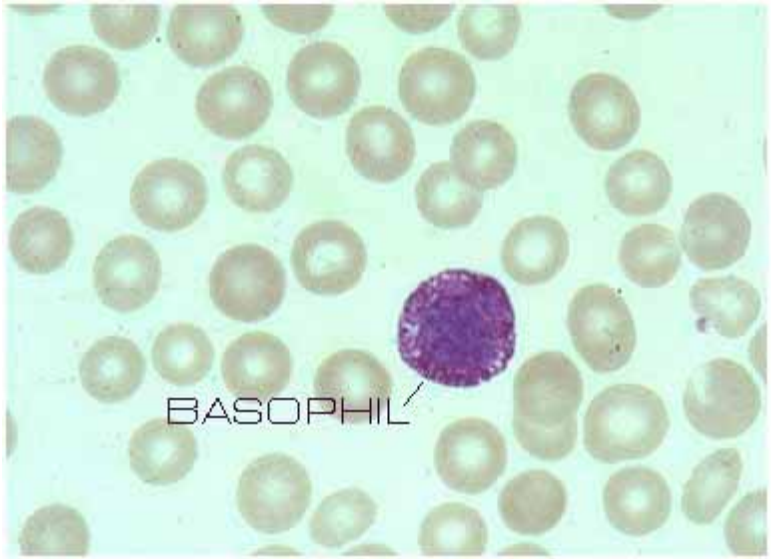
White Blood Cells

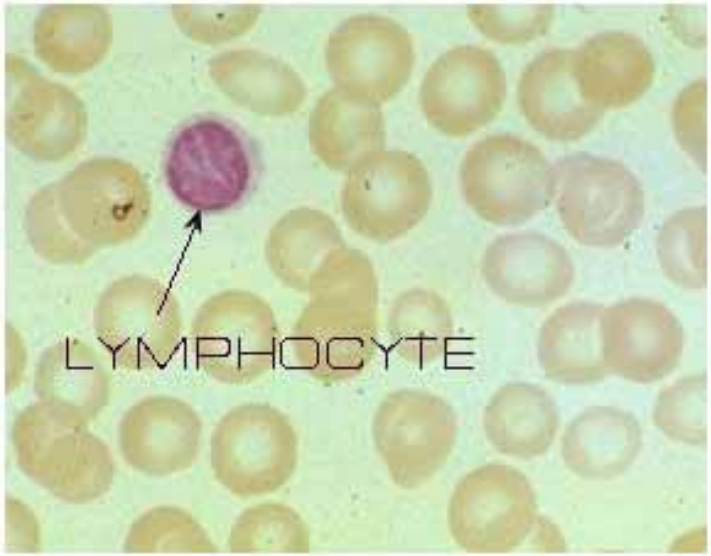
- There are five types of white blood cell
  - neutrophils (中性球) 40 - 75 %
  - Eosinophils (嗜酸性球) 5 %
  - basophils (嗜鹼性球) 0.5 %
  - lymphocytes (淋巴球)20 - 50 %
  - Monocytes (單核球) 1 - 5 %
- Neutrophils, eosinophils and basophils are collectively known as **granulocytes** due to prominent granules in their cytoplasm.

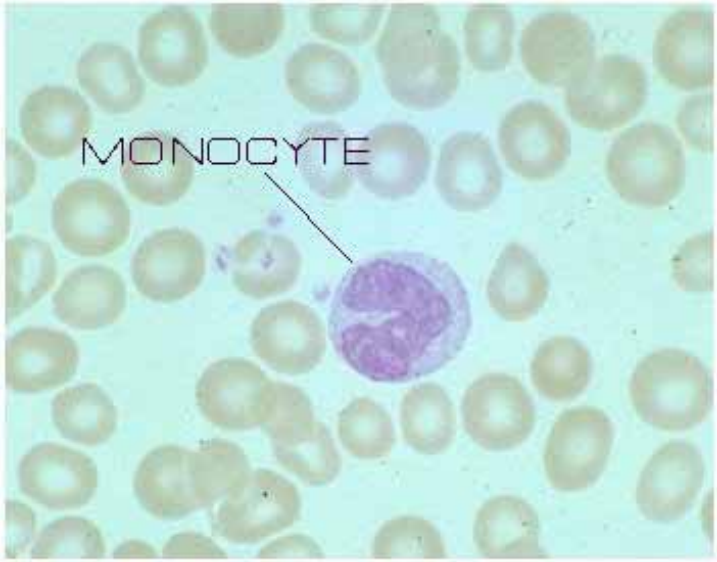


Neutrophils


EOSINOPHIL


BASOPHIL


LYMPHOCYTE


MONOCYTE

The Villi in the Small Intestine

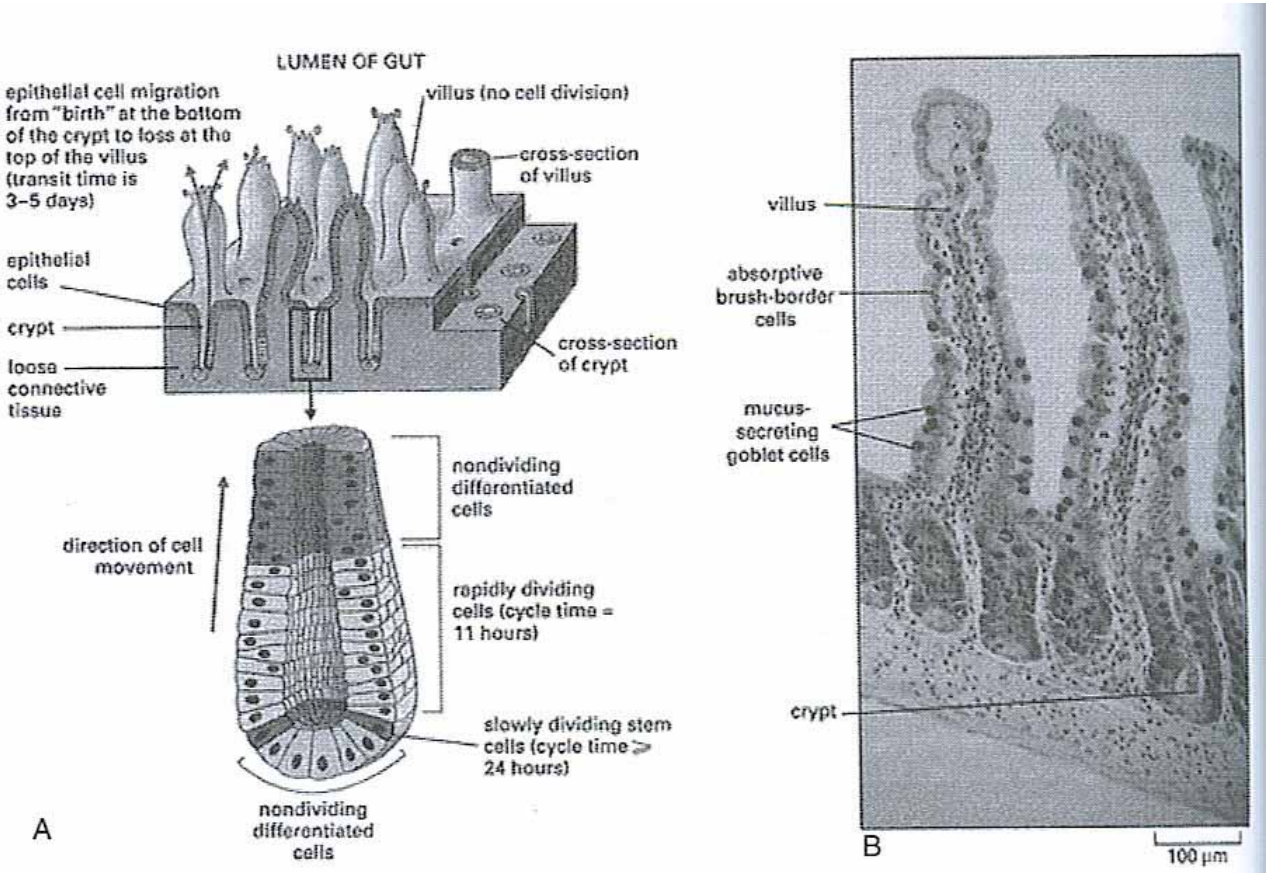


Fig. 12.7 Villi in the small intestine. (A) Rows of villi of epithelial intestinal cells (the diameter of a villi is about 80 μm). (B) A schematic showing the villi and the crypt indicating the mitotic state of the cells in various locations (from Alberts *et al.*, 1994).

Tissue Formation

Human Development

- Pre-embryonic period (first 2 weeks)
  - includes cleavage, implantation and gastrulation (原腸形成)
- Embryonic period (3rd - 8th week)
  - includes induction of organ systems
- Fetal period (3rd to 9th month)
  - includes growth and development

Tissue Repair

Wound Healing

- The entire wound healing process is a complex series of events that begins at the moment of injury and can continue for months to years.

Phases of Wound Healing

I. Inflammatory Phase

A) Immediate to 2-5 days

B) Hemostasis (止血)

Vasoconstriction

Platelet aggregation

Thromboplastin (血栓形成素) makes clot

C) Inflammation

Vasodilation

Phagocytosis

II. Proliferative Phase

A) 2 days to 3 weeks

B) Granulation (肉芽)

Fibroblasts lay bed of collagen

Fills defect and produces new capillaries

C) Contraction

Wound edges pull together to reduce defect

D) Epithelialization (上皮化)

Crosses moist surface

Cell travel about 3 cm from point of origin in all directions

III. Remodeling Phase

A) 3 weeks to 2 years

B) New collagen forms which increases tensile strength to wounds

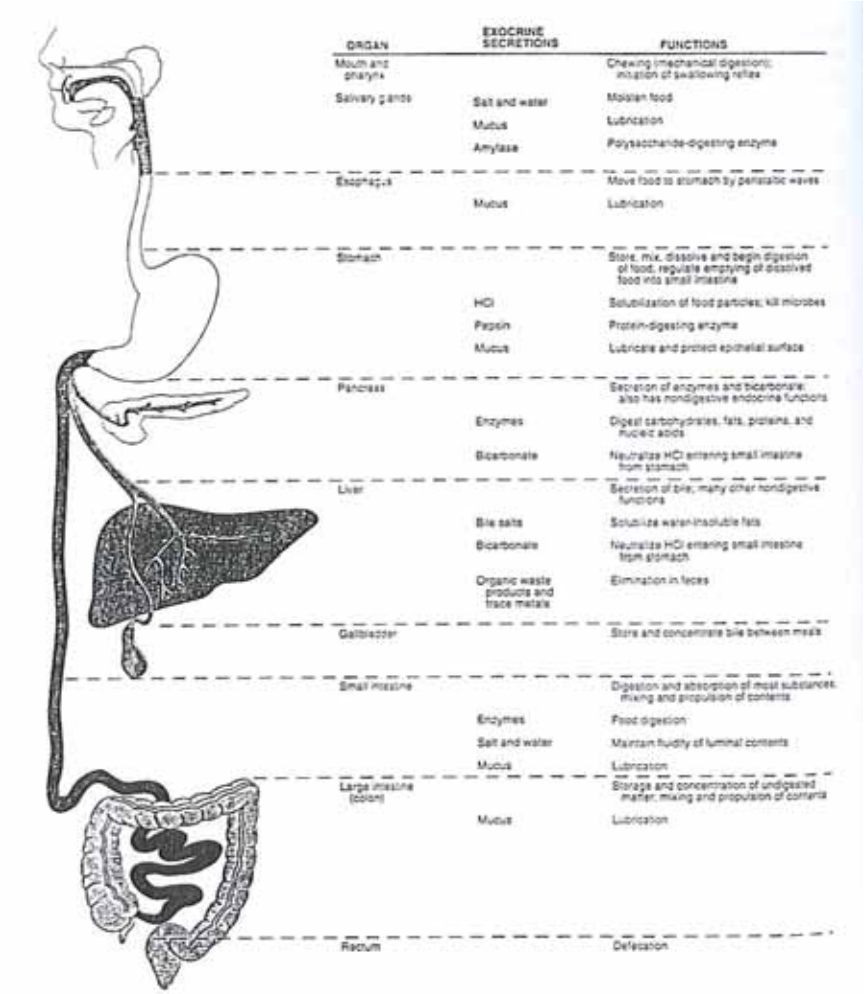
C) Scar tissue is only 80 percent as strong as original tissue

Organization of Tissues into Functional Subunits

TABLE 12.4 The Major Organ Systems of the Body

Circulatory	Heart, blood vessels, blood (some classifications also include lymphatic vessels and lymph in this system)	Transport of blood throughout the body's tissues
Respiratory	Nose, pharynx, larynx, trachea, bronchi, lungs	Exchange of carbon dioxide and oxygen; regulation of hydrogen–ion concentration
Digestive	Mouth, pharynx, esophagus, stomach, intestines, salivary glands, pancreas, liver, gallbladder	Digestion and absorption of organic nutrients, salts, and water
Urinary	Kidneys, ureters, bladder, urethra	Regulation of plasma composition through controlled excretion of salts, water, and organic wastes
Musculoskeletal	Cartilage, bone, ligaments, tendons, joints, skeletal muscle	Support, protection, and movement of the body; production of blood cells
Immune	Spleen, thymus, and other lymphoid tissues	Defense against foreign invaders; return of extracellular fluid to blood; formation of white blood cells
Nervous	Brain, spinal cord, peripheral nerves and ganglia, special sense organs	Regulation and coordination of many activities in the body; detection of changes in the internal and external environments; states of consciousness; learning; cognition
Endocrine	All glands secreting hormones: Pancreas, testes, ovaries, hypothalamus, kidneys, pitutitary, thyroid, parathyroid, adrenal, intestinal, thymus, heart, pineal	Regulation and coordination of many activities in the body
Reproductive	Male: Tetses, penis, and associated ducts and glands	Production of sperm; transfer of sperm to female
	Female: Ovaries, uterine tubes, uterus, vagina, mammary glands	Production of eggs; provision of a nutritive environment for the developing embryo and fetus; nutrition of the infant
Integumentary	Skin	Protection against injury and dehydration; defense against foreign invaders; regulation of temperature

The Gastrointestinal Organs



ORGAN	EXOCRINE SECRETIONS	FUNCTIONS
Mouth and pharynx		Chewing (mechanical digestion); initiation of swallowing reflex
Salivary glands	Salt and water	Moisten food
	Mucus	Lubrication
	Amylase	Polysaccharide-digesting enzyme
Esophagus		Move food to stomach by peristaltic waves
	Mucus	Lubrication
Stomach		Store, mix, dissolve and begin digestion of food; regulate emptying of dissolved food into small intestine
	HCl	Solubilization of food particles; kill microbes
	Pepsin	Protein-digesting enzyme
	Mucus	Lubricate and protect epithelial surface
Pancreas		Secretion of enzymes and bicarbonate; also has nondigestive endocrine functions
	Enzymes	Digest carbohydrates, fats, proteins, and nucleic acids
	Bicarbonate	Neutralize HCl entering small intestine from stomach
Liver		Secretion of bile; many other nondigestive functions
	Bile salts	Solubilize water-insoluble fats
	Bicarbonate	Neutralize HCl entering small intestine from stomach
	Organic waste products and trace metals	Elimination in feces
Gallbladder		Store and concentrate bile between meals
Small intestine		Digestion and absorption of most substances; mixing and propulsion of contents
	Enzymes	Food digestion
	Salt and water	Maintain fluidity of luminal contents
	Mucus	Lubrication
Large intestine (colon)		Storage and concentration of undigested matter; mixing and propulsion of contents
	Mucus	Lubrication
Rectum		Defecation

Fig. 12.9 Functions and organization of the gastrointestinal organs (from Vander *et al.*, 1994).

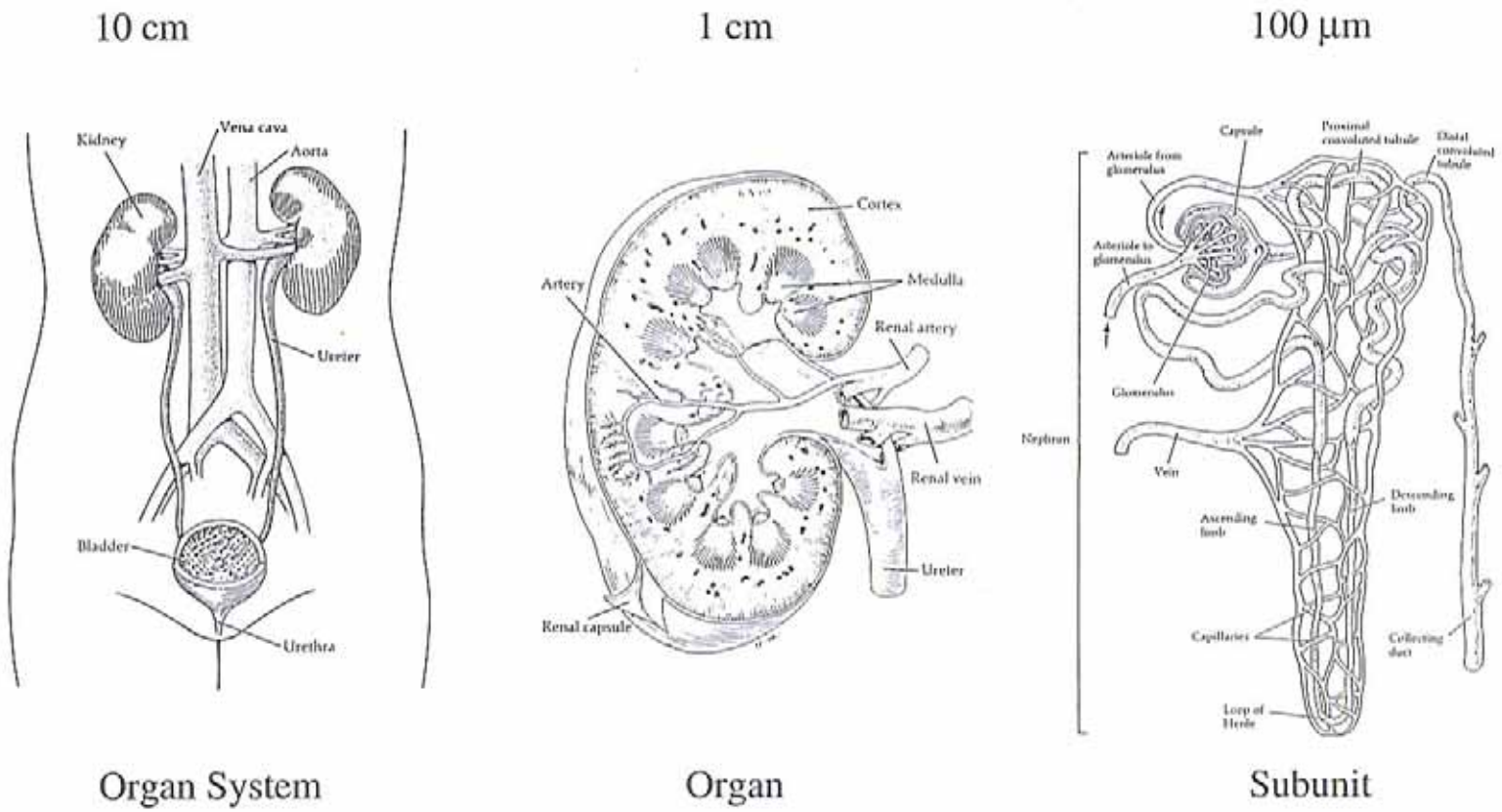


Fig. 12.10 An organ system, an organ, and a functional subunit.

Stem Cells

Customized embryonic stem cells

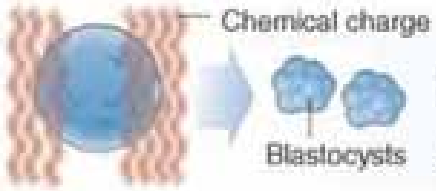
South Korean scientists have created the first human embryonic stem cells that are a genetic match to patients with spinal cord injuries and other diseases, a step in research that might one day lead to growing replacement tissue to treat diseases.

Get a sample

DNA from skin cells was collected from 11 male and female patients ages 2 to 56 with spinal cord injuries, diabetes or a congenital immune disease

Nuclear transfer

The cells were then inserted into donated eggs whose genes were removed



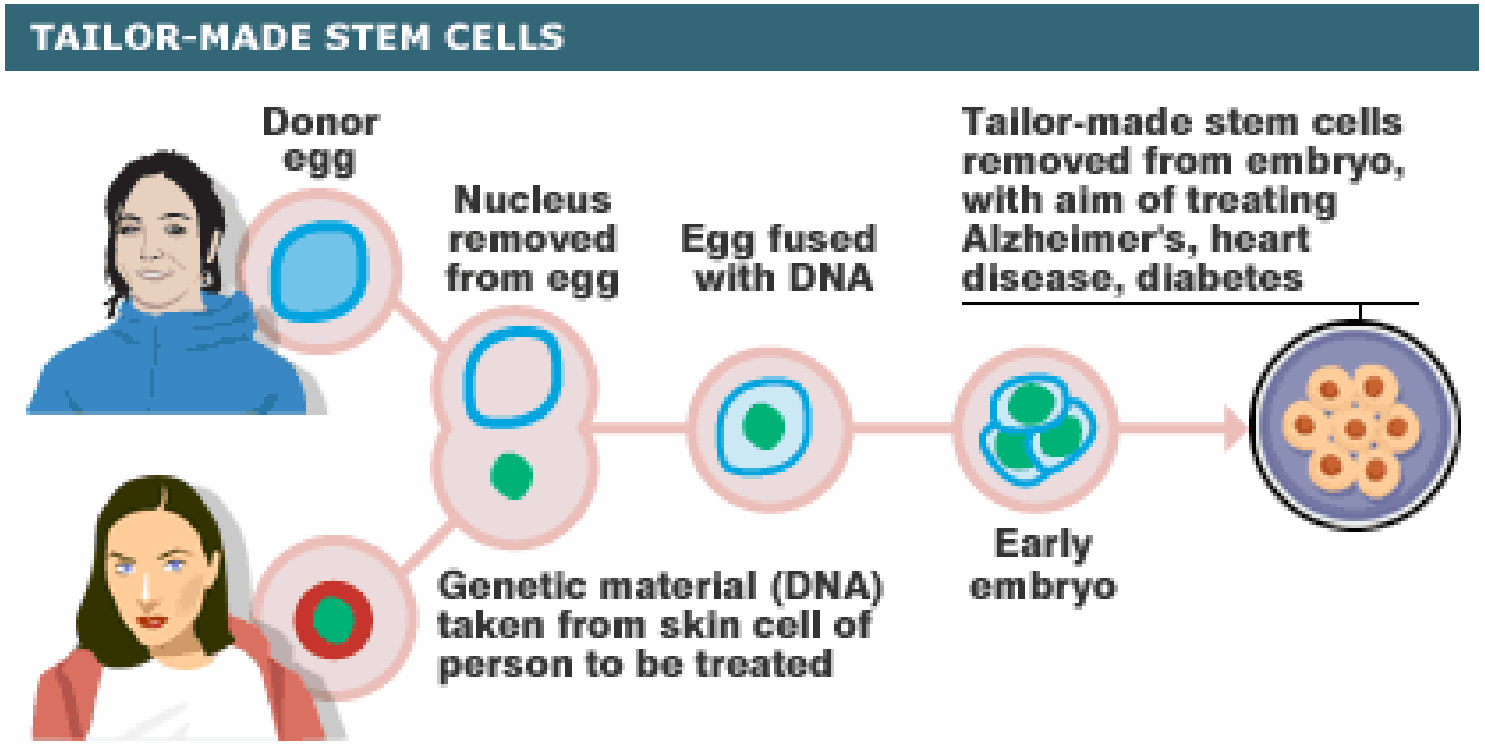
Grow cells

Chemicals jump-started cellular division and 31 early stage embryos, called blastocysts, grew

From the blastocysts, scientists harvested 11 "lines" of stem cells – each a genetic match to the donor of the skin cells

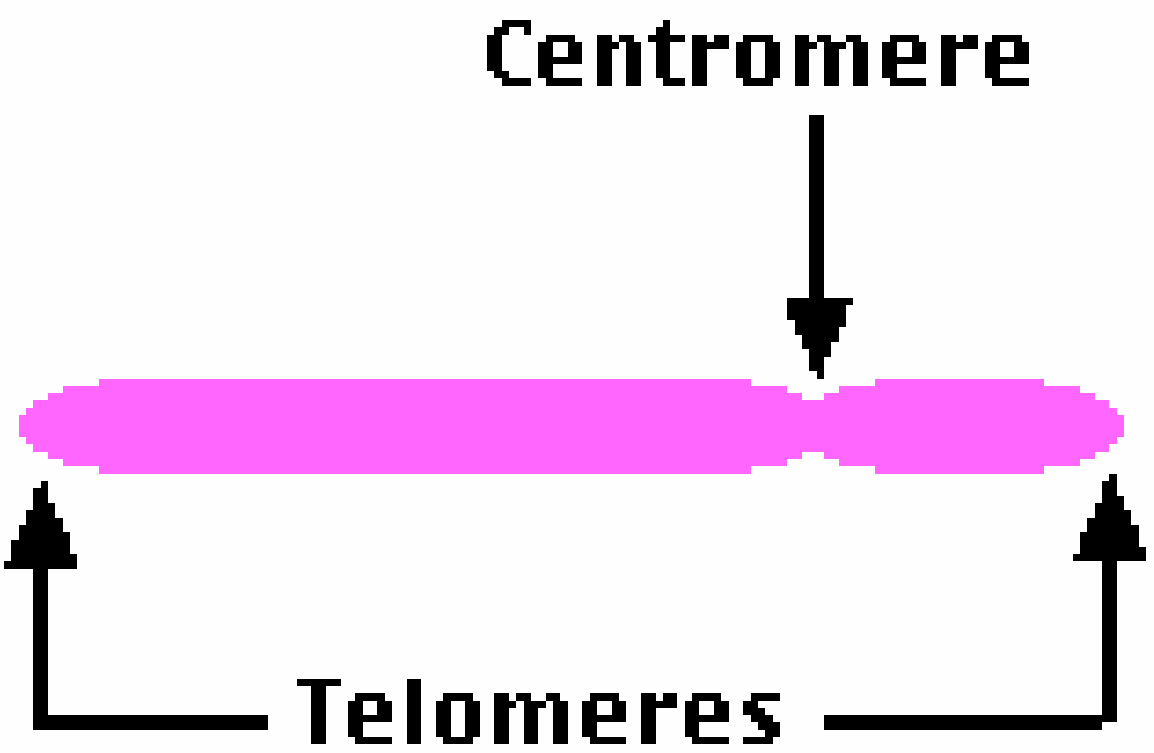
SOURCE: Science

AP

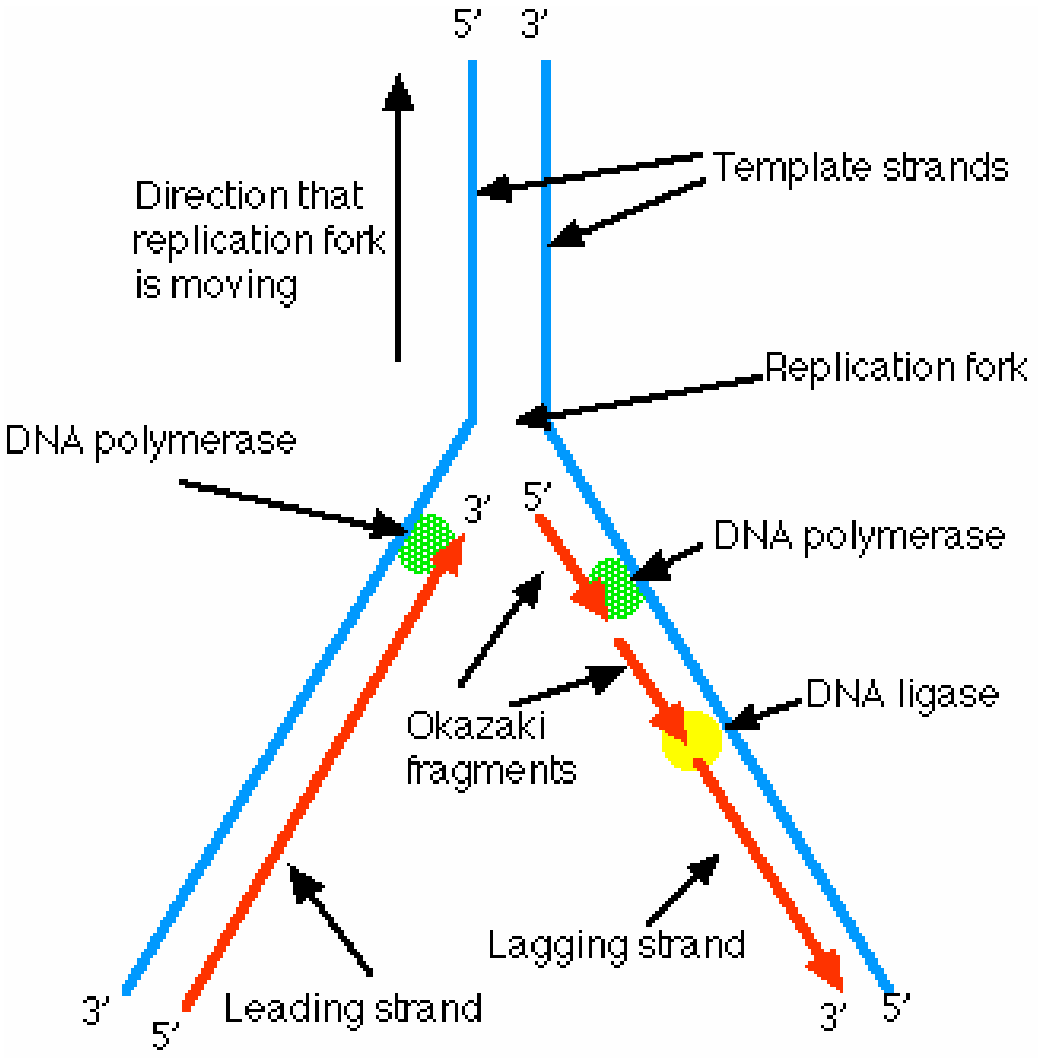

TAILOR-MADE STEM CELLS
Donor egg
Nucleus removed from egg
Egg fused with DNA
Tailor-made stem cells removed from embryo, with aim of treating Alzheimer's, heart disease, diabetes
Early embryo
Genetic material (DNA) taken from skin cell of person to be treated

Stem Cell Aging

- Telomeres
  - Linear chromosomes have noncoding repeating sequences on their ends
  - Normal human somatic cells lack of telomerase activity and the telomeres are shortened by about 50-200 bp per replication
- Telomerase
  - A ribonucleoprotein DNA polymerase
  - Elongate telomeres in eukaryotes


Centromere
Telomeres

DNA Replication



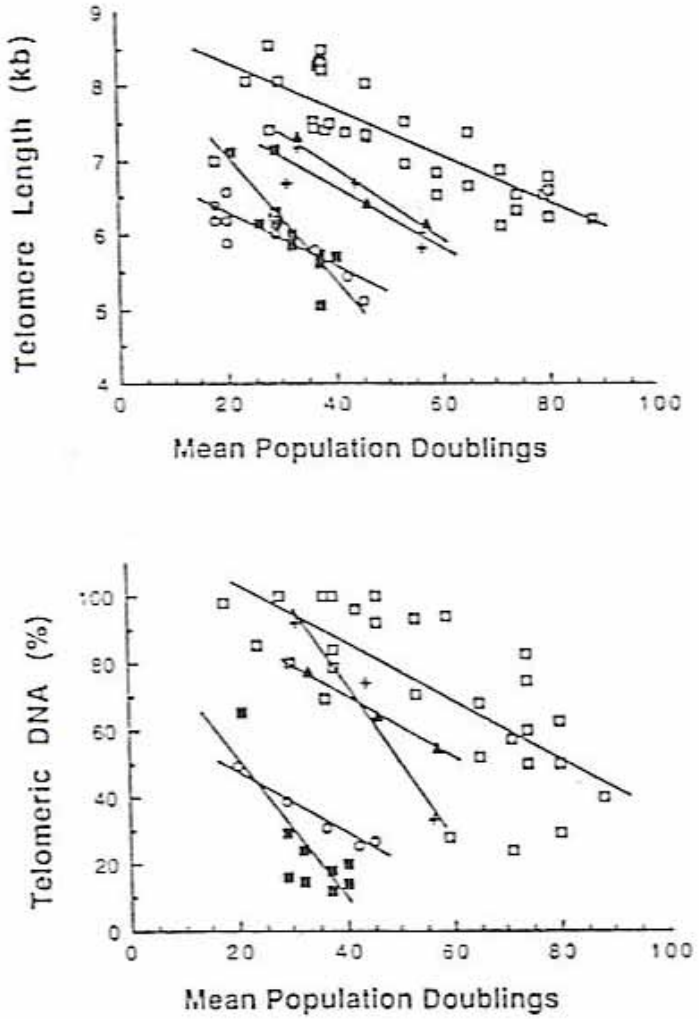


Fig. 12.16 Primary experimental data showing the shortening of telomere length with increasing cellular doubling in cell culture (from Harley et al., 1990).

Cell Differentiation

- A process by which a cell undergoes phenotypic changes to an overtly specialized cell type
- A carefully orchestrated switching off and on of gene families

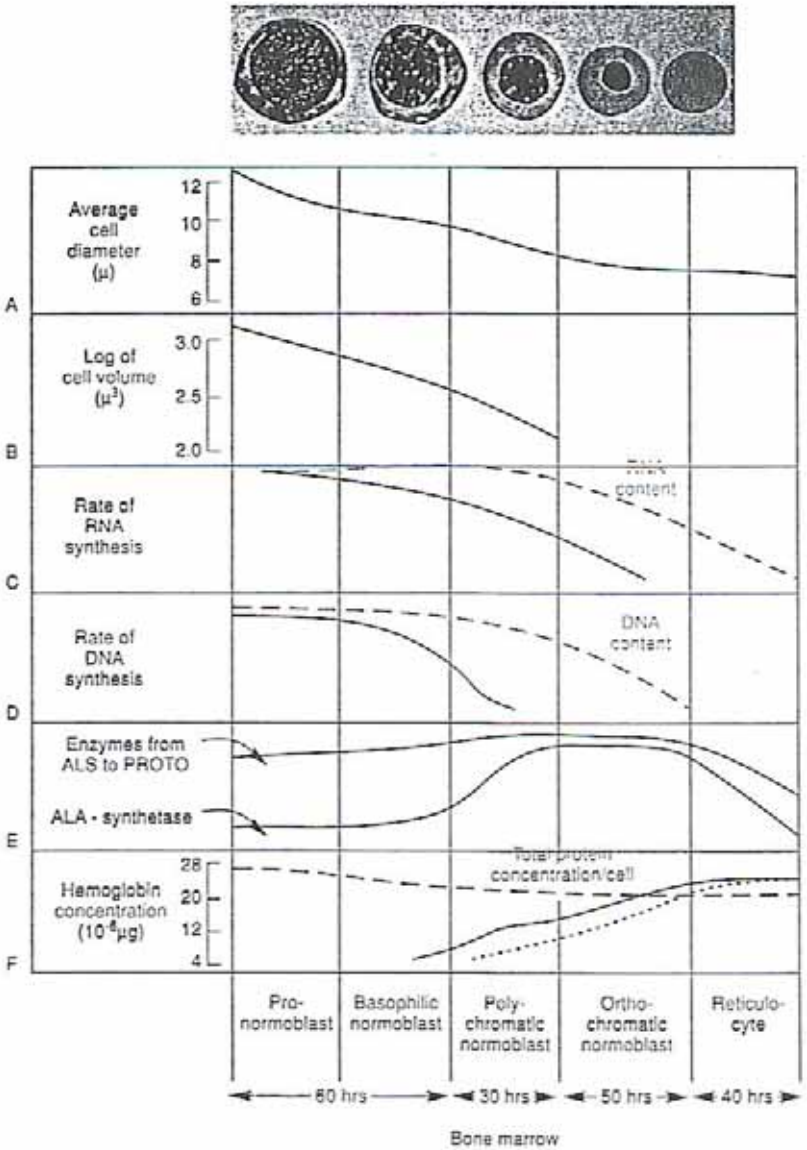


Fig. 12.17 Erythroid maturation sequence (from Granich and Levere, 1964).

Experimental Observation of Differentiation

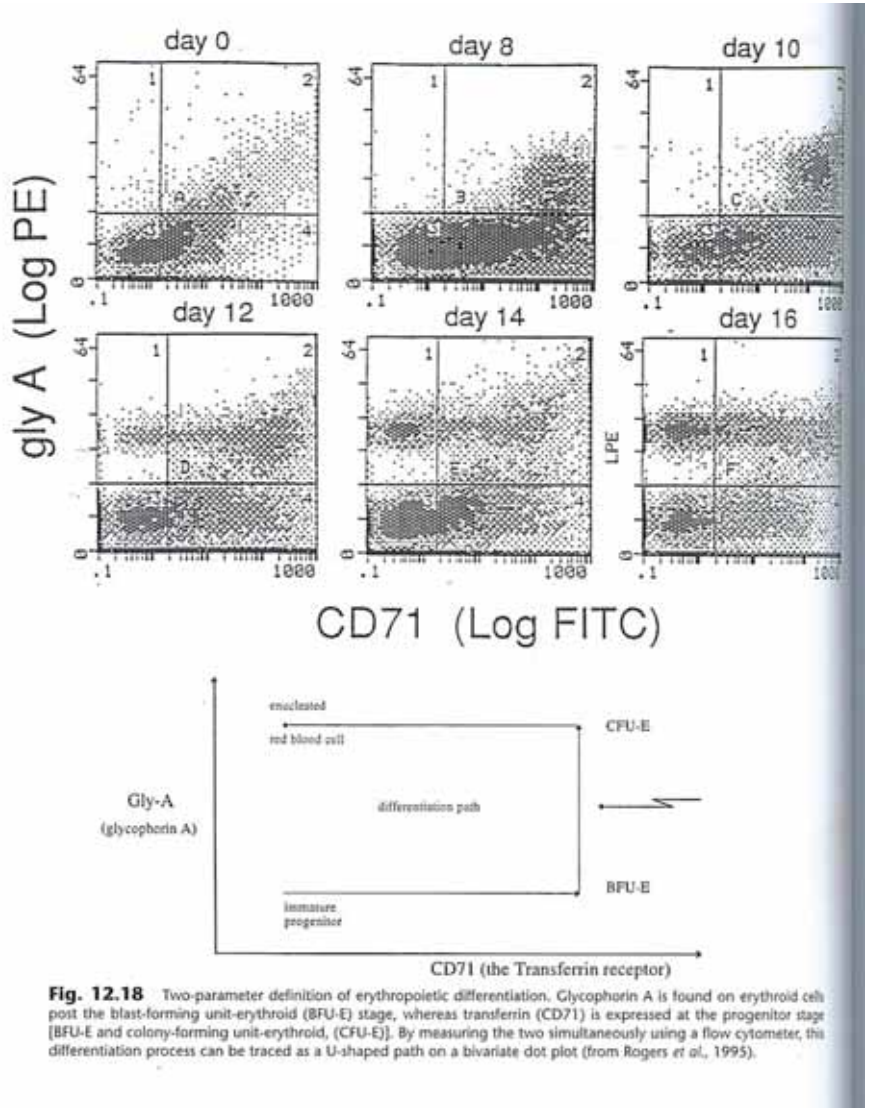


Fig. 12.18 Two-parameter definition of erythropoietic differentiation. Glycophorin A is found on erythroid cells post the blast-forming unit-erythroid (BFU-E) stage, whereas transferrin (CD71) is expressed at the progenitor stage [BFU-E and colony-forming unit-erythroid, (CFU-E)]. By measuring the two simultaneously using a flow cytometer, this differentiation process can be traced as a U-shaped path on a bivariate dot plot (from Rogers *et al.*, 1995).

Two Different Approaches of the Kinetics of Cell Differentiation

- Compartmental Models

- Differentiation as a Continuous Process

Cell Migration is Important During

- Organogenesis
- Embryonic development
- Tissue repair
  - wound healing
  - angiogenesis
- Immune system
- Cancer Metastasis

Cell Motion is a Random Walk Process

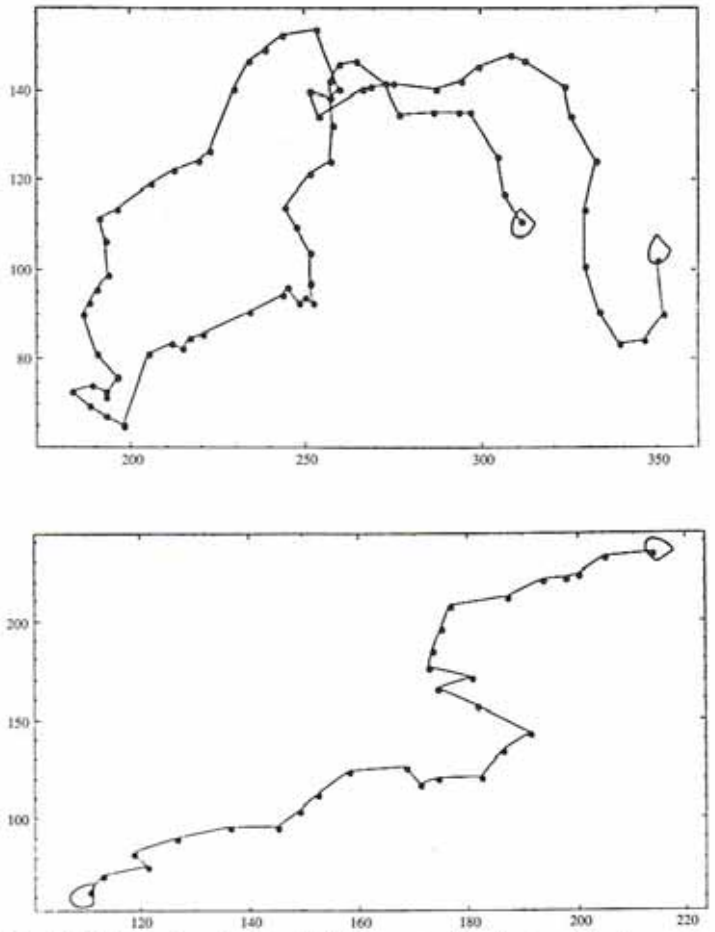
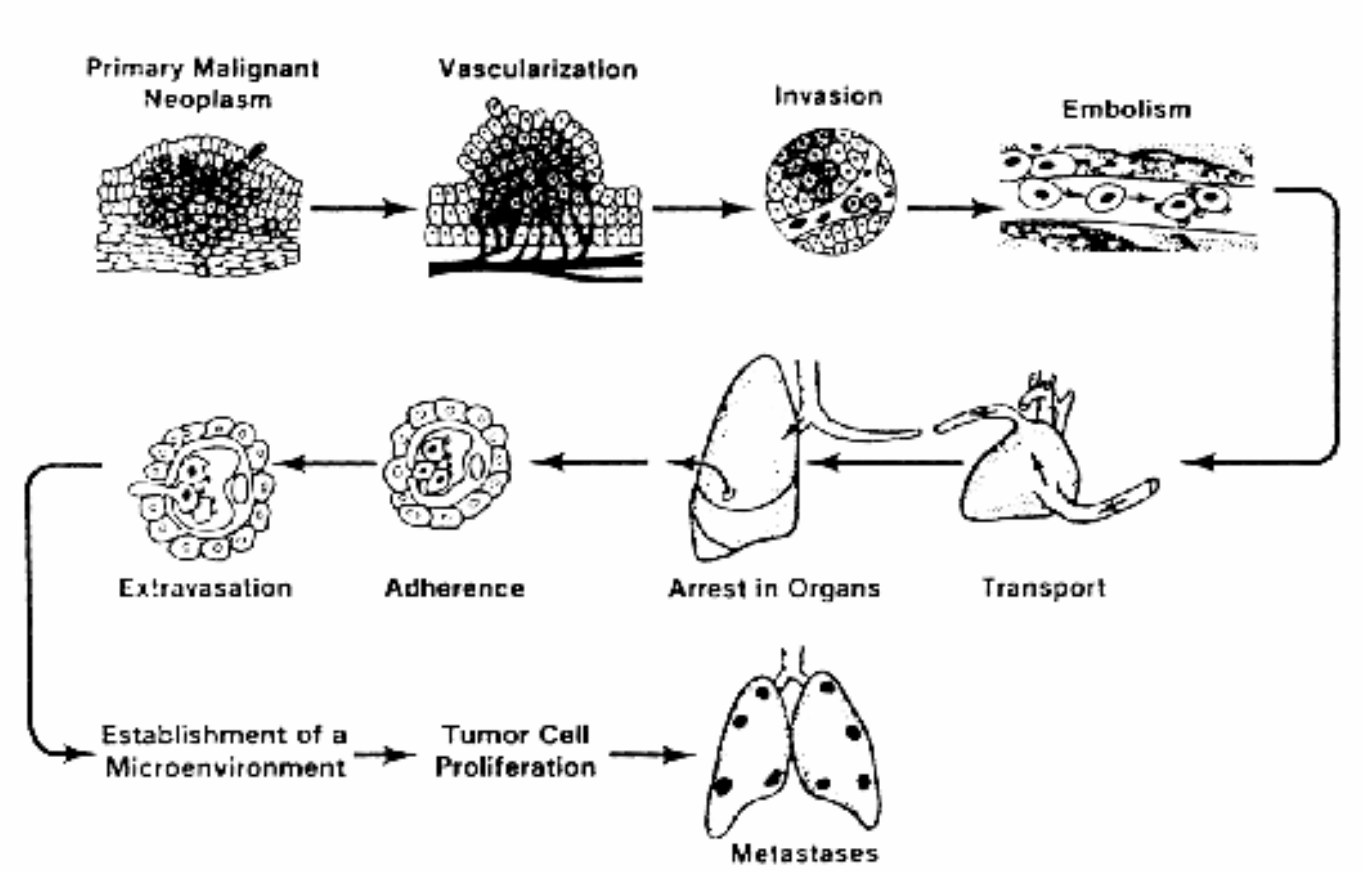


Fig. 12.19 Experimental paths of individual neutrophil leukocytes undergoing random motility in uniform environments (from Lauffenburger and Linderman, 1993).

TABLE 12.6 Random Motion — Measured Cell Speeds and Persistence Times

Cell Type	Speed	Persistence Time
Rabbit neutrophils	20 μm/min	4 min
Rat alveolar macrophages	2 μm/min	30 min
Mouse fibroblasts	30 μm/h	1h
Human microvessel endothelial cells	25–30 μm/h	4–5 h

Cancer Metastasis



Cell Cycle

$$dX/dt + v\, dX/da = \alpha(a)x \qquad (12.8)$$

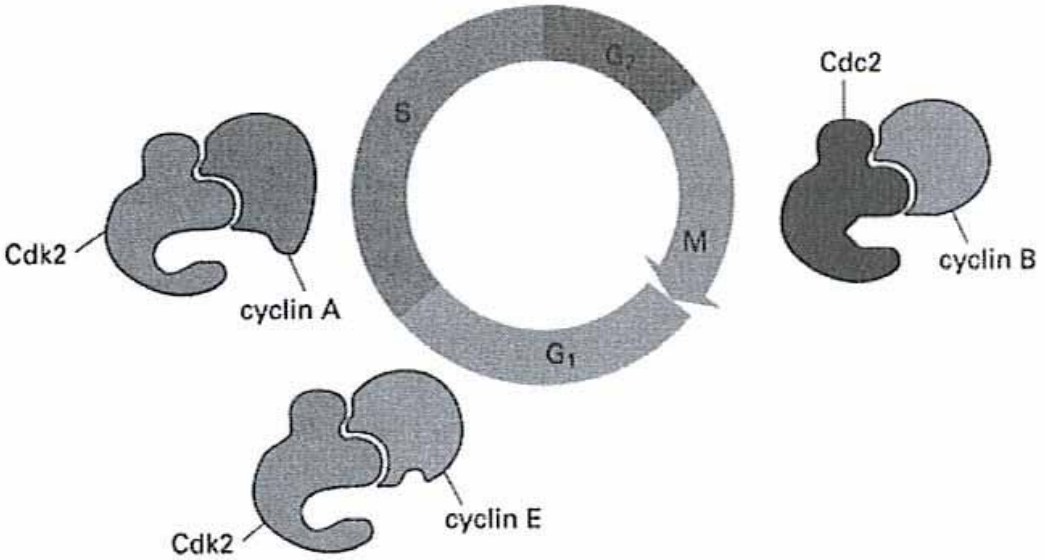


Fig. 12.20 Schematic representation of the eukariotic cell cycle (G_1–S–G_2–M) and the presence of cycling-dependent kinases.

- Changes in cell number of cellular processes are equal to:

  Entry by input – differentiation – exit by apoptosis + entry by cell division

How Do Cells Communicate?

- They secrete soluble signals, knowns as cyto- and chemokines
- They touch each other and communicate via cell-cell contact
- They make proteins that alter the chemical microenvironment (extracellular matrix)

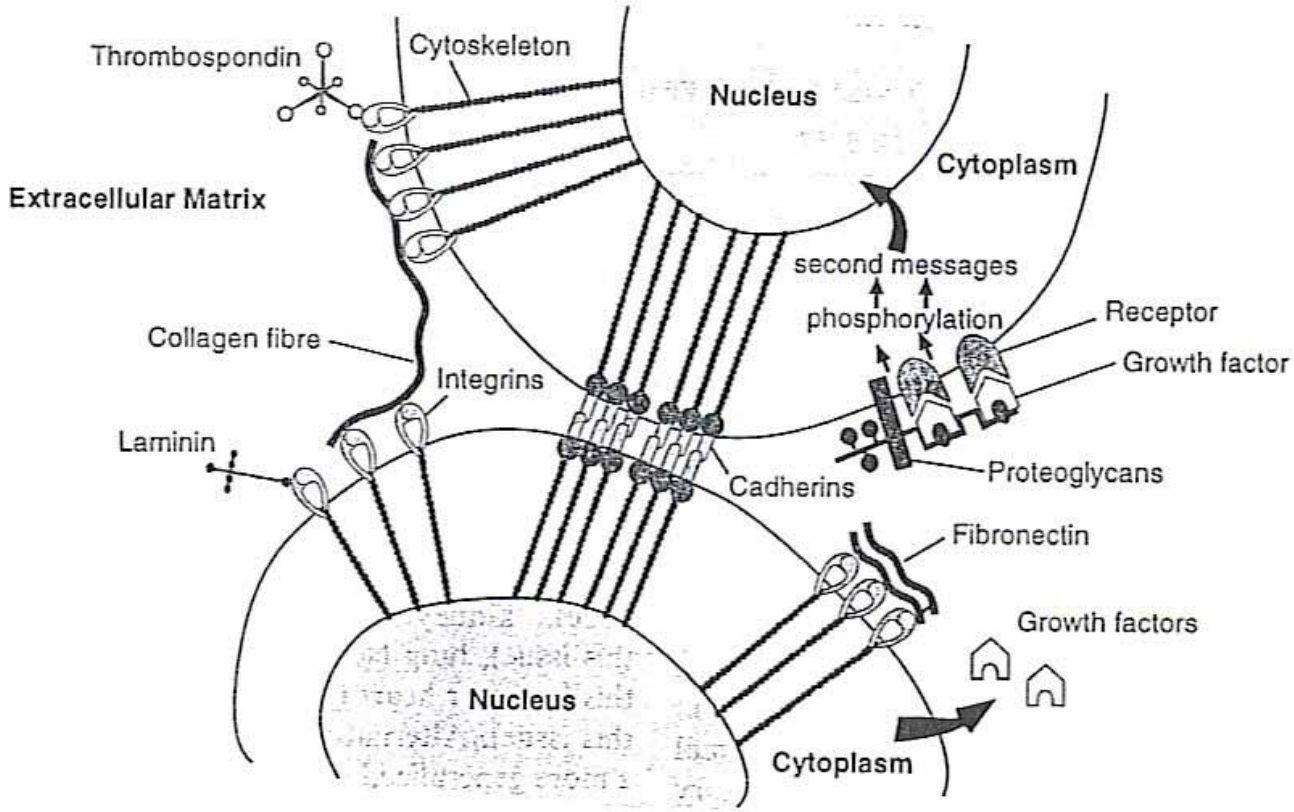


Fig. 12.21 Cell and extracellular matrix (ECM) protein interactions (from Mutsaers *et al.*, 1997).

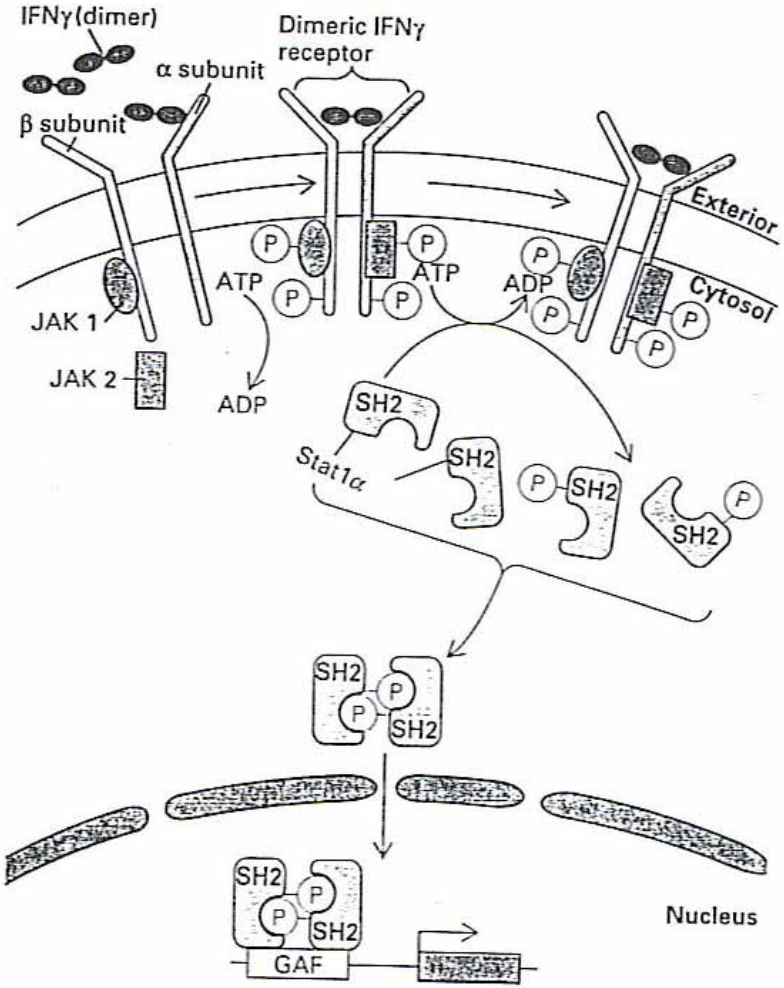


Fig. 12.23 A schematic representation of the interferon gamma signal transduction pathway (from Lodish *et al.,* 1995).

Extracellular Matrix

TABLE 12.7 Components of the Extracellular Matrix[a]

Component	Function	Location
Collagens	Tissue architecture, tensile strength Cell–matrix interactions Matrix–matrix interactions	Ubiquitously distributed
Elastin	Tissue architecture and elasticity	Tissues requiring elasticity, e.g., lung, blood vessels, heart, skin
Proteoglycans	Cell–matrix interactions Matrix–matrix interactions Cell proliferation Binding and storage of growth factors	Ubiquitously distributed
Hyaluronan	Cell–matrix interactions Matrix–matrix interactions Cell proliferation Cell migration	Ubiquitously distributed
Laminin	Basement membrane component Cell migration	Basement membranes
Epiligrin	Basement membrane component (epithelium)	Basement membranes
Entactin (nidogen)	Basement membrane component	Basement membranes
Fibronectin	Tissue architecture Cell–matrix interactions Matrix–matrix interactions Cell proliferation Cell migration Opsonin	Ubiquitously distributed
Vitronectin	Cell–matrix interactions Matrix–matrix interactions Hemostasis	Blood Sites of wound formation
Fibrinogen	Cell proliferation Cell migration Hemostasis	Blood Sites of wound formation
Fibrillin	Microfibrillar component of elastic fibers	Tissues requiring elasticity, e.g., lung, blood vessels, heart, skin
Tenascin	Modulates cell–matrix interaction Antiadhesive Antiproliferative	Transiently expressed associated with remodeling matrix
SPARC[b] (osteonectin)	Modulates cell–matrix interaction Antiadhesive Antiproliferative	Transiently expressed associated with remodeing matrix
Thrombospodin	Modulates cell–matrix interaction	Platelet α granules
Adhesion molecules	Cell surface proteins mediating cell adhesion to matrix or adjacent cells Mediators of transmembrane signals	Ubiquitously distributed
von Willebrand factor	Mediates platelet adhesion Carrier for procoagulant factor VIII	Plasma protein Subendothelium

[a] Mutsaers, S., Bishop, J., McGrouther, G., and Laurent, G., "Mechanisms of Tissue Repair, from Wound Healing to Fibrosis," Int. J. of Biochem. Cell Biol. Vol. 29 No. 1 (p. 5–17) (1997).
[b] SPARC, secreted protein acidic and rich in cysteine.

The Microenvironment is Characterized by

- Neighboring cells

  Cell-cell contact, soluble growth factors, etc

- The chemical environment

  The extracellular matrix, the dynamics of the nutritional environment

- The local geometry

TABLE 12.9 Cells That Contribute to the Tissue Microenvironment

Stromal cells: derivates of a common precursor cell
Messenchyme
Fibroblasts
Myofibroblasts
Osteogenic/chondrogenic cells
Adipocytes
Stromal-associated cells: histogenically distinct from stromal cells, permanent residents of a tissue
Endothelial cells
Macrophages
Transient cells: cells that migrate into a tissue for host defense either prior to or following an inflammatory stimulus
Blymphocytes/plasma cells
Cytotoxic T cells and natural killer (NK) cells
Granulocytes
Parenchymal cells: cells that occupy most of the tissue volume, express functions that are definitive for the tissue, and interact with all other cell types to facilitate the expression of differentiated function

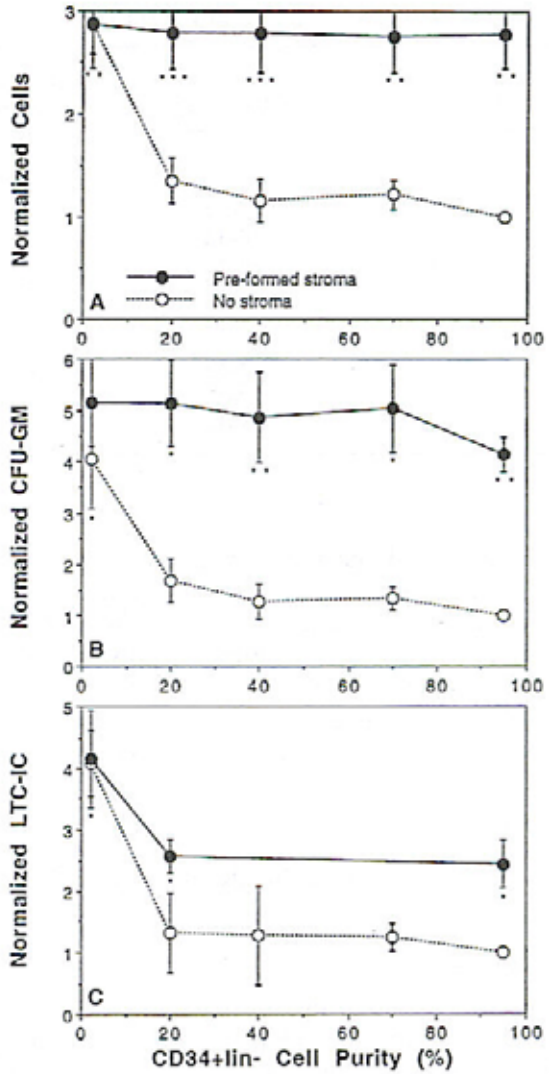


Fig. 12.27 Effect of $CD34^{+}$lin cell (a population of primitive hematopoietic cells) purity on culture output. With increasing purity the performance on a per cell basis drops due to loss of accessory cell function. CFU-GM, colony-forming units granulocyte/macrophage, LTC-IC, long-term culture-initiating cells (from Koller *et al.*, 1995a).

Oxygenation

TABLE 12.11 Measured Oxygen-Demand Rates of Human Cells in Culture

Human	μmol $O_2/10^6$ cells/h
HeLa	0.1–0.0047
HLM (liver)	0.37
LIR (liver)	0.30
AM-57 (amnion)	0.045–0.13
Skin fibroblast	0.064
Detroit 6 (bone marrow)	0.43
Conjunctiva	0.28
Leukemia MCN	0.22
Lymphoblastoid (namalioa)	0.053
Lung	0.24
Intestine	0.40
Diploid embryo WI-38	0.15
MAF-E	0.38
FS-4	0.05

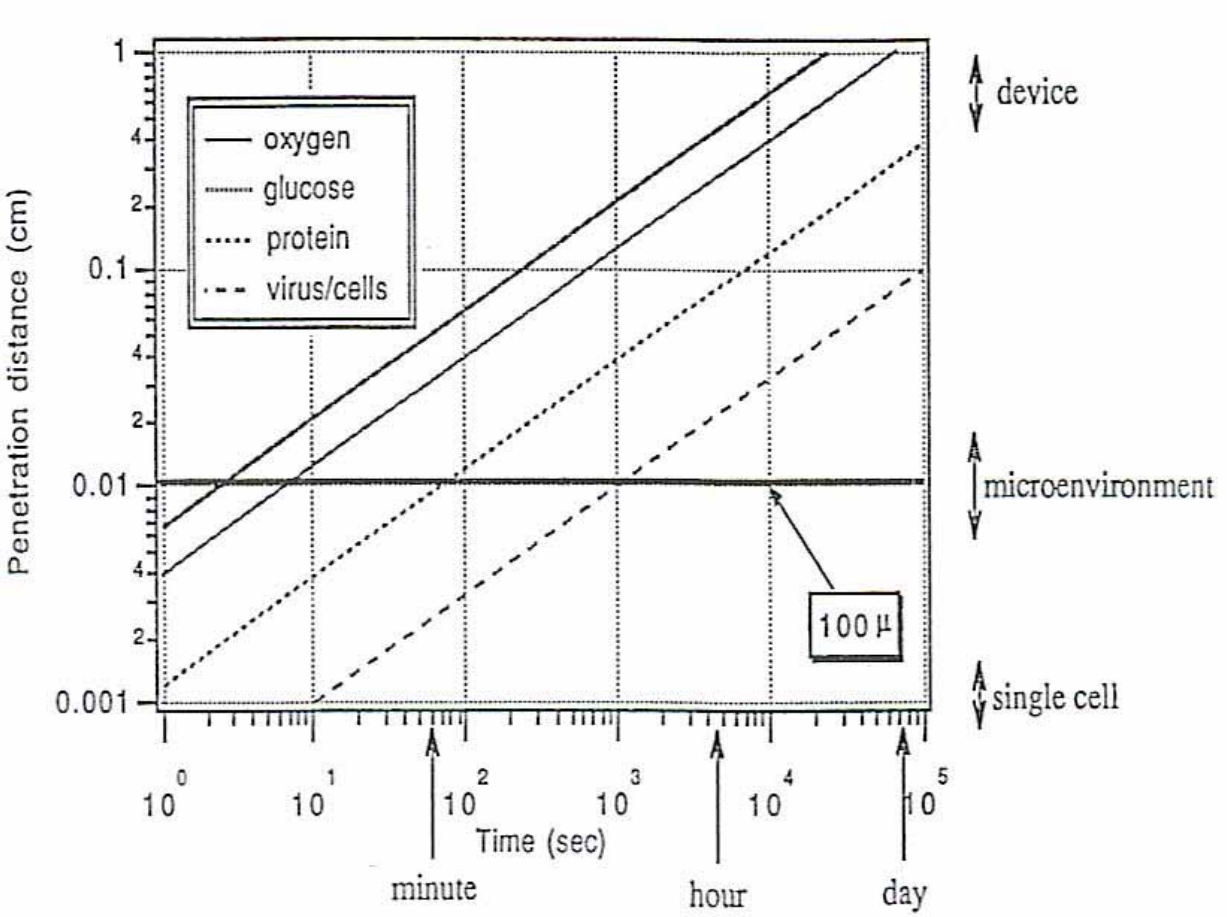


Fig. 12.28 The diffusional penetration lengths as a function of time for several classes of biomolecules.

Key Design Challenges of Scaling Up

- Oxygenation-providing adequate flux of oxygen at physiology concentrations
- Provision and removal of cyto- and chemokines
- Physiological perfusion rates and uniformity in distribution
- Biomaterials-functional, structural, toxicity and manufacturing characteristics

In Situ Respirometer

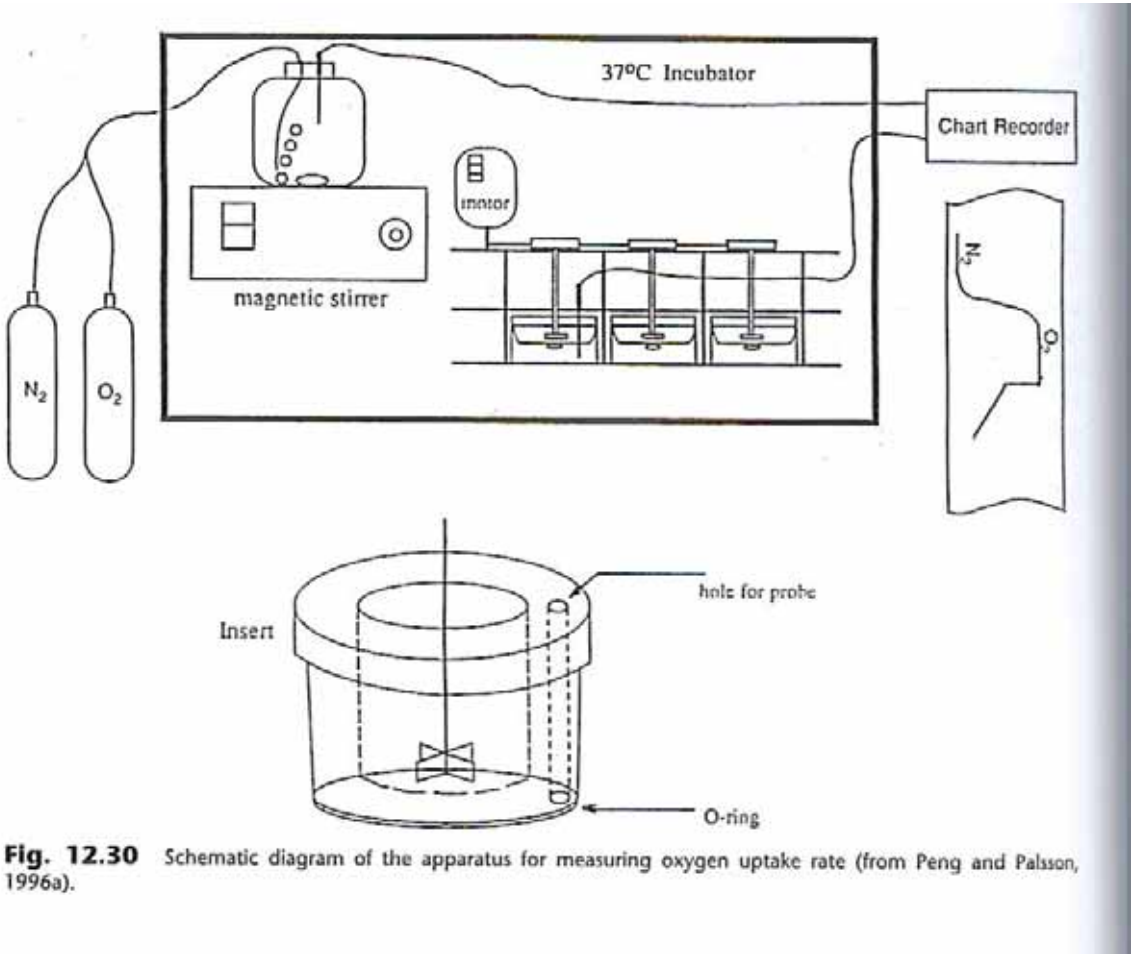
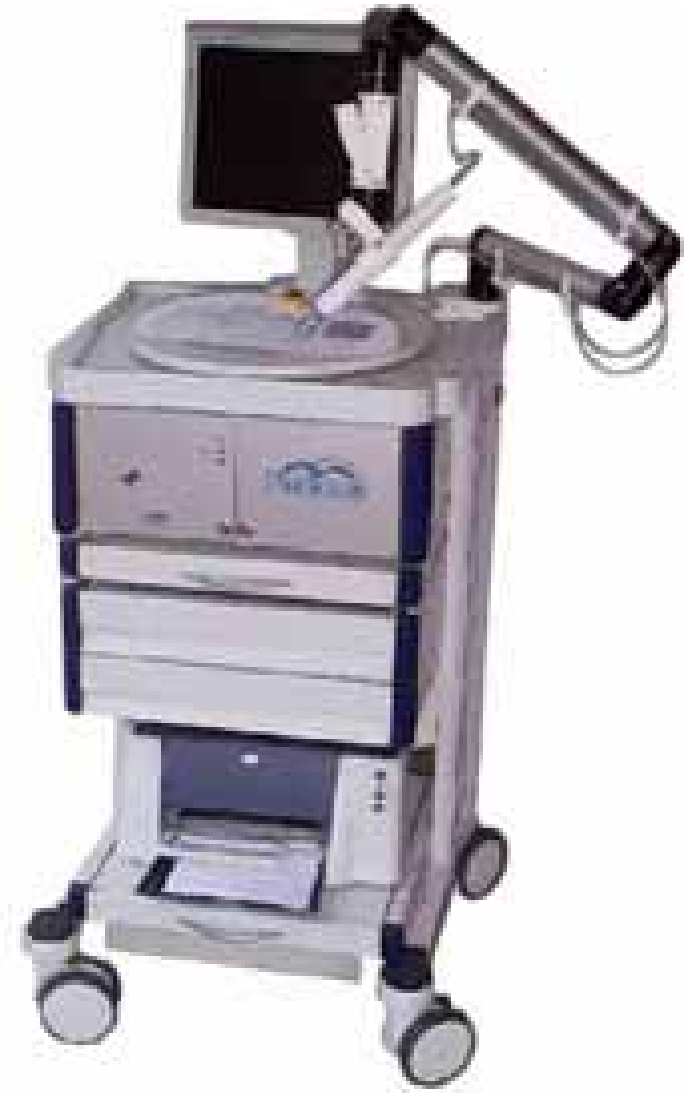
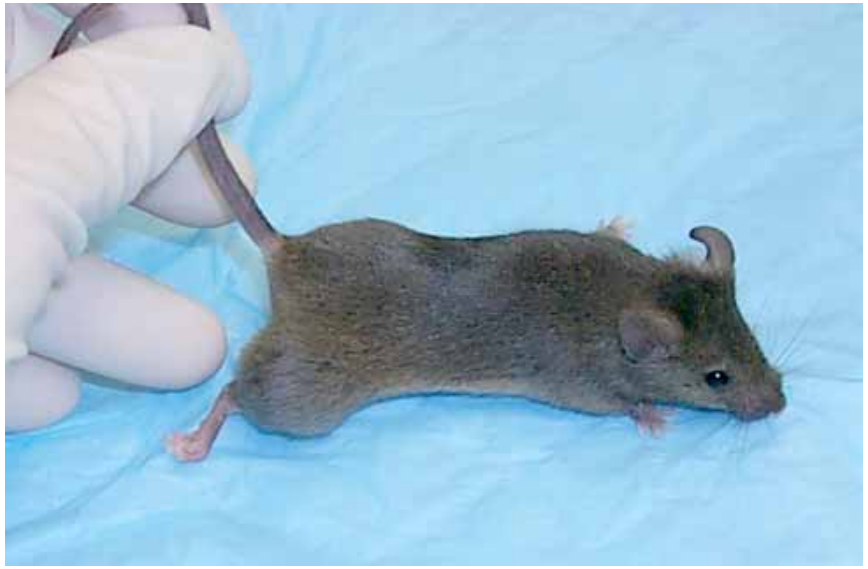


Fig. 12.30 Schematic diagram of the apparatus for measuring oxygen uptake rate (from Peng and Palsson, 1996a).

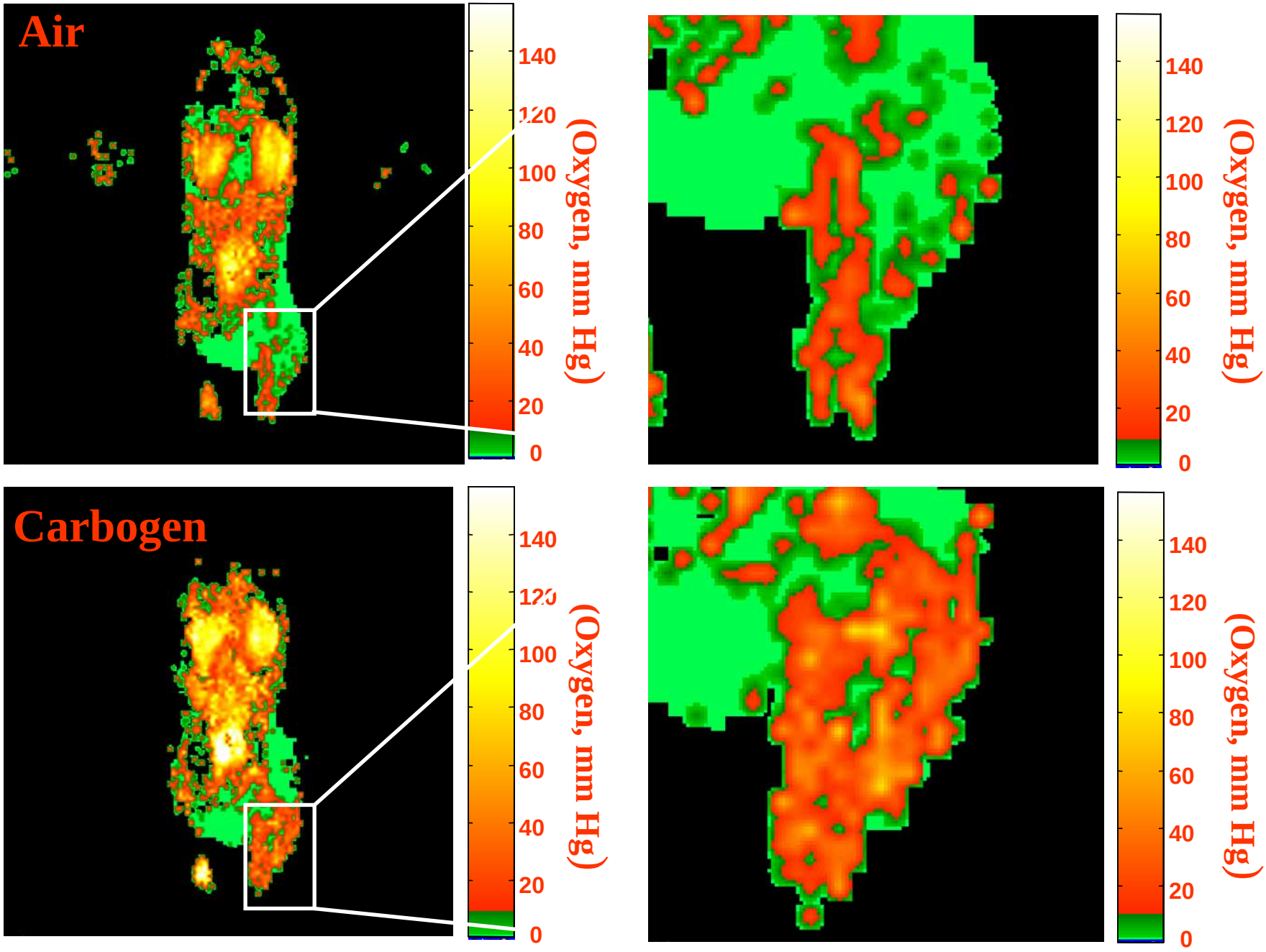
Microelectrode pO_2 Historgraph



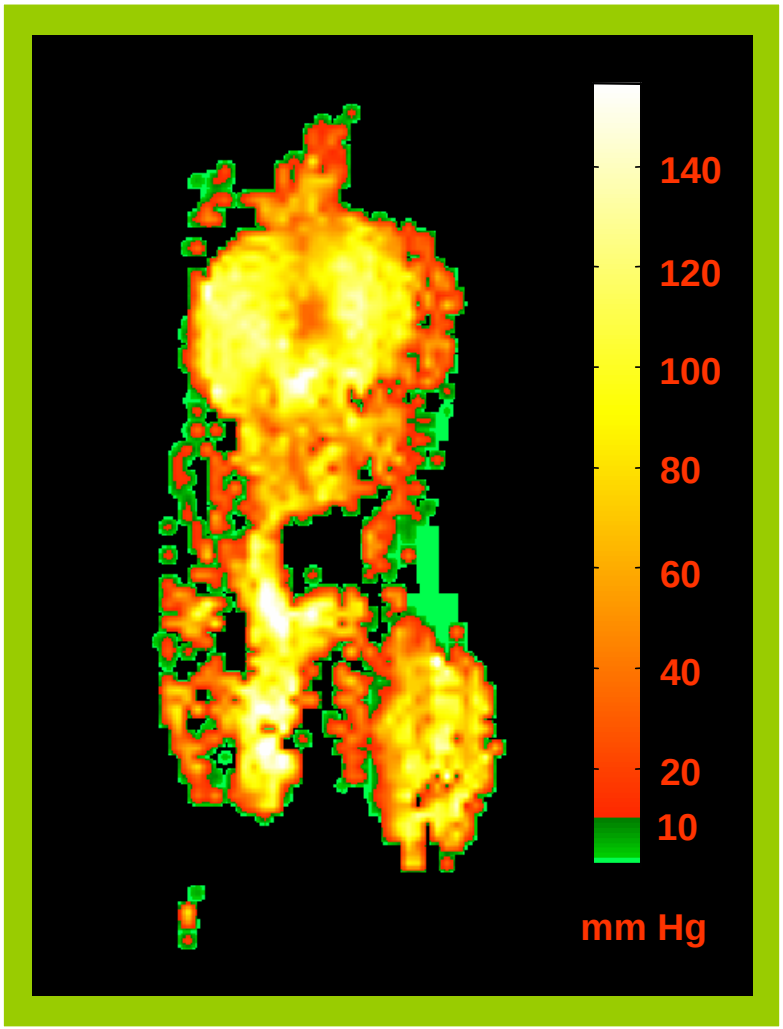
1cm SCC Tumor



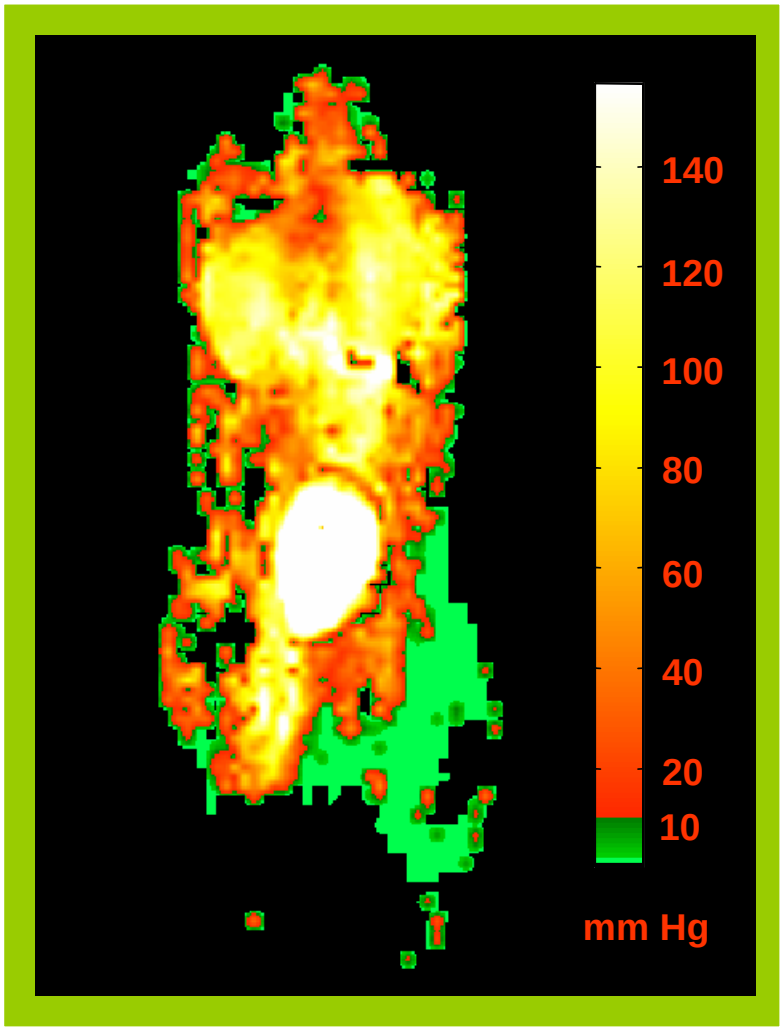
OMRI: SCC Tumor



Breathing Carbogen
15 Gy Tumor Irradiation
pO_2 Maps



Before XRT



100 min. After 15 Gy

Fluid Flow

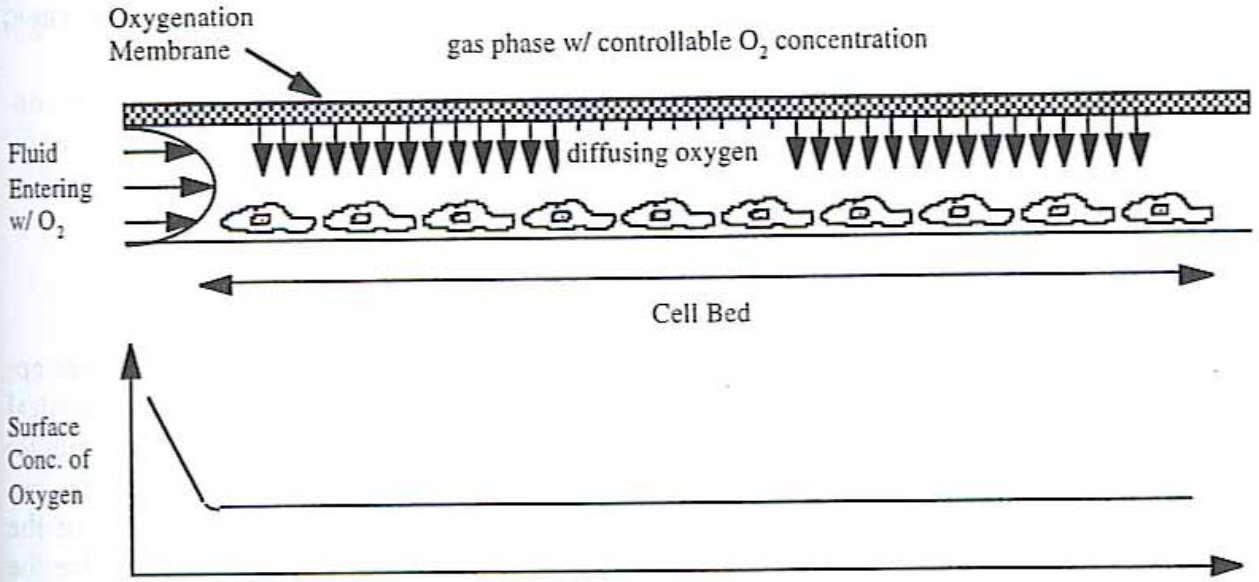


Fig. 12.31 Oxygen delivery across a membrane that is placed on top of a fluid that is flowing across a cell bed. If the fluid transit time is much slower than the diffusional time for oxygen, then oxygen is delivered primarily via diffusion. This leads to a small entrance effect where the oxygen in the incoming stream is consumed while the oxygen concentration over the rest of the cell bed is relatively constant.

Uniformity

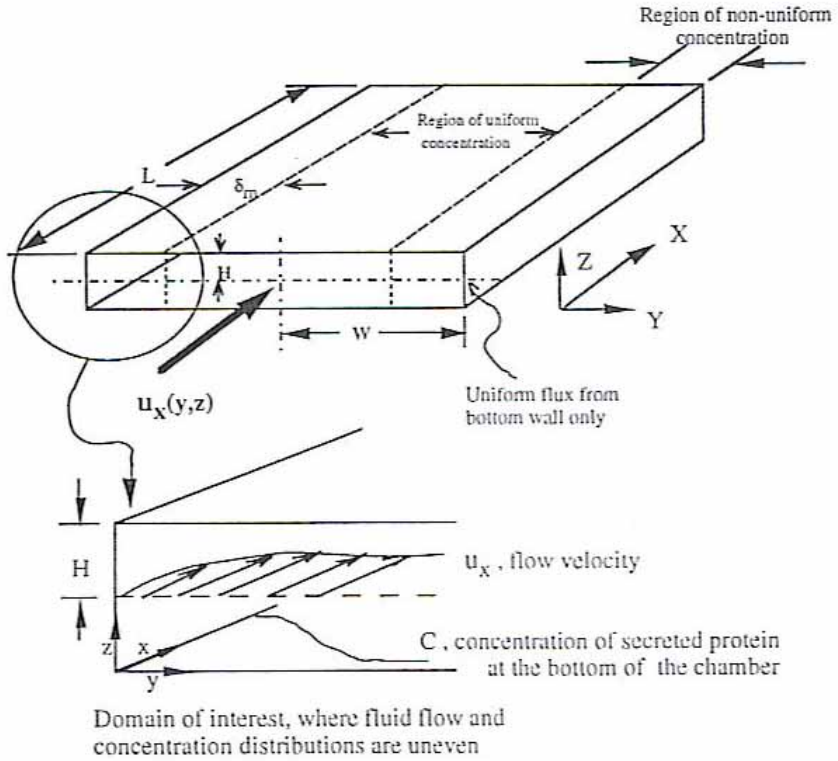


Fig. 12.32 Coordinate system for a rectangular chamber with production of biological factors secreted by cells lodged on the bottom wall. The fluid is slowed down close to the side wall creating a different concentration than that found in the middle of the slit. This leads to a very different microenvironment for cell growth and development of tissue function at the wall than elsewhere in the chamber (from Peng and Palsson, 1996b).

Problems of Delivering Cellular Therapies in a Clinical Setting

- Donor-to-donor variability
- Strongly interacting variables
- Immune rejection
- Tissue procurement

Exercises

- Please discuss a new method to measure oxygen tension in tissues other than OMRI or pO2 microelectrode
- Please describe details of DNA replication process
- Please explain why the tissue microenvironment is important for tissue engineering