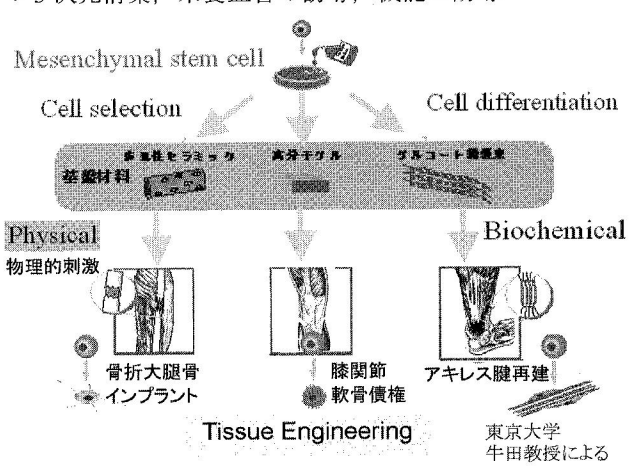
バイオエンジニアリング技術ロードマップ
マイクロ・ナノバイオメカニクス「荷重支持組織の再生医療への応用を中心に」

バイオエンジニアリング部門　東北大学　山口　隆美

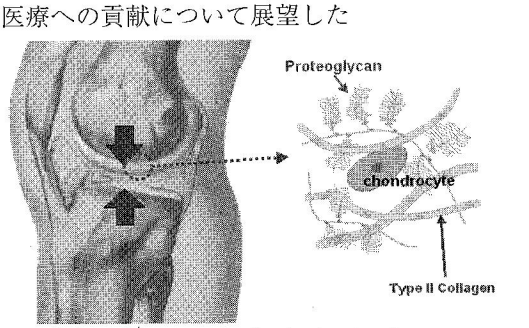
■ロードマップ作成検討分野
＊人工臓器（人工心臓，人工関節，…）
＊健康福祉機器・用具
＊マイクロナノバイオエンジニアリング再生医療（ティッシューエンジニアリング）
＊生命・生体情報（バイオインフォマティクス）イメージング（ミクロ・マクロ）
＊コンピューテーショナルバイオエンジニアリング etc

■マイクロ・ナノバイオメカニクス
細胞・組織レベルの力学現象と生物学現象の相互作用解明
＊生物学の問題：
・適応，リモデリング，遺伝子発現の調節，化学的修飾
＊力学の問題：
・せん断応力，力（静水圧，静的および動的）

■ティッシューエンジニアリング
＊ティッシュー（Tissue：組織）とは何か
→細胞が集合して，一定の機能を発揮する構造
・細胞，細胞間質（matrix），血管
＊生体組織の階層性
分子－細胞小器官－細胞－組織－器官－系－体
＊3 次元構築，栄養血管の誘導，機能の誘導

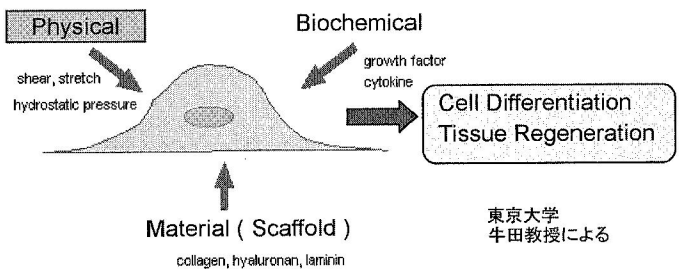


■趣旨
近年，細胞を人工物と混和し，これに生化学的・物理的刺激を加えることで所望の組織に分化させ，治療に応用する再生医療への期待が高まっている．ところで，荷重支持組織（骨，腱・靭帯，軟骨，動脈など）あるいは力発生組織（筋肉，心筋，消化管など）の形態や機能の維持には適切な力学刺激が必須であることが明らかとなってきており，組織再生には力学刺激の考慮が不可欠である．このような観点から機械工学の再生医療への貢献について展望した

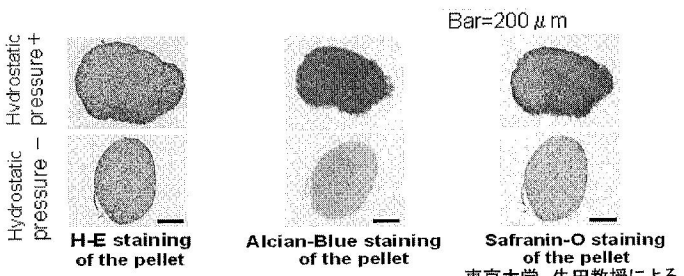


Hydrostatic pressure loading to chondrocytes by weight or moving　東京大学　牛田教授による

■技術課題に対する社会的・技術的ニーズ
＊機能の失われた生体組織を新たな組織で置き換えたい．
＊荷重支持組織の再生を考える上で，力学刺激を考慮することが必要である．
＊再生組織内に細胞や基質を 3 次元的に自由配置したい．
＊未分化細胞の分化誘導や生体組織の形態形成（全体の形成だけでなく，血管系の走行なども）に力学環境が密接に関与している．細胞分化と組織再生を支配する力学因子を明らかにする必要がある．



3 Essential Factors in Vitro Tissue Regeneration



Effect of Hydrostatic Pressure Loading On Matrices Production in Chondrocyte Pellets

■キーパラメータの高度化を実現するメカニズムの可能性
＊再生組織のレベル：細胞，組織，器官．
＊ES 細胞や骨髄性幹細胞の分化誘導や組織再生に必要な生化学刺激条件と物理刺激条件の組合せが明らかになり始め，2 次元組織内で細胞の配向を制御する技術，各種成長因子を用い毛細血管網を誘導する技術確立（2005～）
＊細胞の分化誘導や組織再生に必要な刺激条件が更に明らかになり，3 次元組織内で細胞の配向を制御する技術，各種成長因子と力学刺激の組合せにより，毛細血管網をある程度の深さにまで誘導する技術が確立される（2010～）
＊幾つかの大規模組織・器官の再生に関し適切な刺激条件が判り，3 次元組織の中心部にまで毛細血管網を走行させる技術が確立される（2015～）
＊多くの大規模組織・器官の再生に関し，適切な刺激条件が判る（2020～）

■将来の社会に対する展望
＊動物実験で再生された天然組織と遜色ない組織の出現．
＊ヒトに移植できる天然組織と遜色ない再生組織の出現．
＊本人細胞から再生された天然組織と遜色ない組織出現．

■バイオエンジニアリング部門　技術ロードマップ WG
山口隆美（東北大）　松本健郎（名工大）
和田成生（大阪大）　坂本二郎（金沢大）
中西義孝（九州大）　協力　牛田多加志（東京大）

Micro- and Nano-Biomechanics in Tissue Engineering (Application of Load Bearing Tissues to Regenerative Medicine)

(1) Aims

Recently, the promise of regenerated tissue as a medical treatment in which biological and engineering approaches are combined has been realized through advances in and cross-disciplinary research in biochemical and physical sciences. In order to maintain the form and function of load bearing tissues (such as bones, tendons, ligaments, cartilage, and arteries) and power generating tissues (such as muscles, heart muscles, and the digestive tract tissues), proper mechanical stimulation needs to be maintained. This is especially true for tissue regeneration. From this point-of-view, we project the potential contribution of mechanical engineering to the field of tissue regeneration.

(2) Social and technical needs

- To be able to replace biological tissues in which function has been lost with new tissues.
- Mechanical stimulation must be taken into consideration in any examination of regeneration of load bearing tissues.
- To be able to rearrange cells and basic structures three-dimensionally in regenerated tissues.
- Need to clarify mechanical factors that control cell differentiation and tissue regeneration as mechanical environments are closely linked to and affect differentiation of premature cells and the formation of living tissues (not only general formation but also vascular organization).

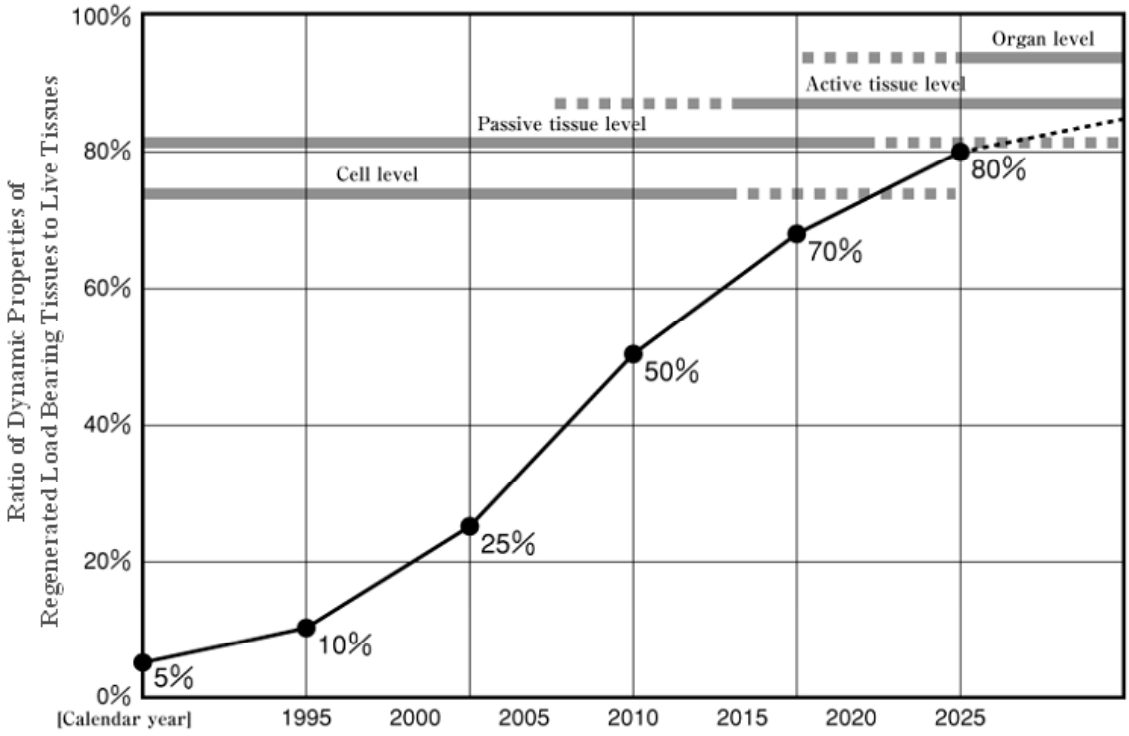
(3) Future directions for determining key mechanisms and parameters

Use of regenerated tissues may be implemented first at the cellular level, then at the tissue level and finally at the organ level.

- Some crucial combinations of biochemical and physical stimulation necessary for the differentiation of ES cells and bone marrow stromal cells to tissue regeneration may be elucidated. Technology for controlling cell orientation in two-dimensional tissues and inducing capillary nets using various growth factors may be established (2005 and later).
- Many of the specific conditions necessary to stimulate cell differentiation and tissue regeneration may be clarified. Technology for controlling cell orientation in three-dimensional tissues and for forming capillary networks at a certain depth by combining growth factors and mechanical stimulations may be established (2010 and later).
- Appropriate stimulation conditions for the regeneration of several large tissues and organs may be clarified, and technology for forming capillary networks within the regenerated tissues may be established (2015 and later).
- Appropriate stimulation conditions for the regeneration of many large tissues and organs may be clarified (2020 and later).

(4) Contributions to society

- Various tissues with functions equivalent to those of natural tissues generated using animals may be available for medical treatment.
- Various tissues with functions equivalent to those of natural tissues may be available for transplantation into humans.
- Various tissues with functions equivalent to those of natural tissues and regenerated from ones' own cells may be available.



Social & Technical Needs

Social and Technical Needs

- To be able to replace biological tissues in which function has been lost with new tissues.
- Mechanical stimulation must be taken into consideration in the examination of regeneration of the load bearing tissues (such as bones, tendons, ligaments, cartilage, arteries, muscles, cardiac muscles, and digestive organs).
- To be able to rearrange cells and basic structures three-dimensionally in regenerated tissues.
- Need to clarify mechanical factors that control cell differentiation of premature cells and the formation of living tissues (not only general formation but also vascular organization).

Technical Breakthrough

2005～2010	・Clarify the basic stimulation conditions necessary for cell ifferentiation and tissue regeneration. ・Establish technology for controlling cell orientation in two-dimensional tissues.
2010～2015	・Clarify stimulation conditions necessary for cell differentiation and tissue regeneration. ・Establish technology for controlling cell orientation in three-dimensional tissues.
2015～2020	・Clarify appropriate stimulation conditions for the regeneration of several large tissues and organs. ・Establish technology for forming capillary networks at a specific depth in three-dimensional tissues.
2020～2025	・Clarify appropriate stimulation conditions for the regeneration of large tissues and organs.

Changes in Society and Markets

2005～2010	・Start medical care system for elderly people over the age of 75 (completed). ・Generate human iPS (induced pluripotent stem) cells (completed). ・Establish method for culturing human ES cells in large quantities.
2010～2015	・Make various tissues with functions equivalent to those of natural tissues reproduced in animal experiments available. ・Establish medical technology for eyesight recovery with artificial retina chips embedded in eyes. ・Implement ability to determine various genome functions from DNA base sequence.
2015～2020	・Transplant various tissues with functions equivalent to those of natural tissues into humans. ・Put transplantation of artificially cultured heart muscle tissues and hepatocytes into practice. ・Regenerate heart muscles and vascular tissues with functions and structures equivalent to those of normal tissues and liver tissue with function equivalent to that of the natural liver.
2020～2025	・Reproduce various tissues with functions equivalent to those of natural tissues from ones' own cells. ・Establish technologies to predict high-order protein structures, interactions of proteins, interactions of DNA and RNA, and other living activities.