領域略称名：ナノバイオメカ
領 域 番 号：７６８

「マイクロ・ナノバイオメカニクスの開拓」

課題番号：15086101

平成15年度～平成19年度科学研究費補助金

（特定領域研究）研究成果報告書

平成２０年５月

領域代表者　和　田　　仁
東北大学大学院工学研究科　教授

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1．はしがき

生命現象の本質的な多様性は，遺伝子のみではなく，細胞をめぐるマイクロあるいはナノスケールの構造と遺伝情報との相互作用によって担われており，その中でも，力学的相互作用の意義は極めて大きい．従って，力学的環境と生命機能の関係を解明することができれば，細胞及び組織の構造と機能をコントロールする手段を見いだせる可能性が高い．また，これを用いることによって，必要な構造と機能をもつ細胞と組織を創成することが可能となる．

そこで本研究では，力学を基礎とし，マイクロ領域である細胞レベル及びナノ領域である生体高分子や細胞内小器官レベルの力学現象を解明し，これに基づいて人工材料の新たな設計指針の開発と創製を行うと共に，生命体の機能と構造を創成ないし再構成する技術を開発することを試みた．

2．研究組織

研究項目 A01：生体マイクロ・ナノ構造のメカニクス

1.「タンパク質モータ Prestin の構造解明」
　代表者 和田 仁（東北大学）　分担者 熊谷 泉（東北大学），池田 勝久（順天堂大学）
2.「内部の微細構造に立脚した細胞の力学特性計測」
　代表者 松本 健郎（名古屋工業大学）　分担者 宮崎 浩（大阪大学），長山 和亮（名古屋工業大学）
3.「再生肝細胞コロニーに形成された毛細胆管構造のマイクロ・ナノバイオメカニクス」
　代表者 谷下 一夫（慶應義塾大学）
　分担者 池田 満里子（慶應義塾大学），工藤 奨（芝浦工業大学），
　　須藤 亮（Massachusetts Institute of Technology，米国）
4.「軟骨組織のマイクロ・ナノ構造における軟骨細胞・周囲組織のメカニクス解明」
　代表者 村上 輝夫（九州大学）
　分担者 澤江 義則（九州大学），中嶋 和弘（九州大学），坂井 伸朗（九州大学）

研究項目 A02：力学的刺激に対するマイクロ・ナノ構造の応答

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　代表者 安達 泰治（京都大学）
　分担者 北條 正樹（京都大学），田中 基嗣（金沢工業大学），冨田 佳宏（神戸大），
　　佐藤 克也（山口大学），坪田 健一（千葉大）
6.「ナノ領域イメージングを用いた血管内皮細胞の焦点接着斑の力学応答ダイナミクス」
　代表者 佐藤 正明（東北大学）
　分担者 大橋 俊朗（東北大学），坂元 尚哉（東北大学），出口 真次（東北大学）
7.「機械センサー活性化におけるマイクロ・ナノ機構の解析」
　代表者 曽我部 正博（名古屋大学）
　分担者 辰巳 仁史（名古屋大学），陳 玲（南京医科大学），早川 公英（JST），
　　平田 宏聡（JST），野村 健（JST），吉村 健二朗（筑波大学）

研究項目 A03：生体マイクロ・ナノ構造制御による組織創製

8.「生体マイクロ・ナノ構造制御による組織創製」
　代表者 牛田 多加志（東京大学）　分担者 陳 国平（物質・材料研究機構 生体材料研究センター）
9.「細胞培養により作製したハイブリッド人工血管の組織構造に及ぼす流体力学的因子の影響」
　代表者 狩野 猛（北海道大学）　分担者 丹羽 光一（東京農業大学）
10.「生体内でのマイクロ・ナノ構造制御による運動系器官の再建」

代表者 高久田 和夫(東京医科歯科大学)
分担者 宗田 大(東京医科歯科大学), 伊藤 總一郎(国際医療福祉大学),
今井 庸二(東京医科歯科大学), 堀江 三喜男(東京工業大学)

研究項目 A04:生体マイクロ・ナノ構造とバイオインフォマティクス

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代表者 田中 正夫(大阪大学) 分担者 松本 健志(大阪大学), 東藤 正浩(北海道大学)
12.「心臓および脳血管病の発症と進展メカニズムの解明」
代表者 山口 隆美(東北大学)
分担者 和田 成生(大阪大学), 坪田 健一(千葉大学), 石川 拓司(東北大学),
今井 陽介(東北大学), 森 大祐(東北大学)
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代表者 田中 英一(名古屋大学) 分担者 水野 幸治(名古屋大学), 山本 創太(名古屋大学)
14.「細胞・細胞内部の損傷現象の解析と医療応用のための血管微細構造のインフォマティクス」
代表者 山田 宏(九州工業大学) 分担者 石黒 博(九州工業大学), 玉川 雅章(九州工業大学)

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	直接経費	間接経費	合計
平成15年度	194,700	0	194,700
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平成19年度	1,500	0	1,500
総計	498,300	0	498,300

4. 研究発表

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4．2．口頭発表

1. オーガナイズセッション
Micro- and Nano-Biomechanics
The first Asia Pacific Conference on Biomechanics とのジョイント
日時:2004 年 3 月 25 – 28 日
場所:大阪大学コンベンションセンター

2. オーガナイズセッション
マイクロ・ナノバイオメカニクス
第 17 回日本機械学会バイオエンジニアリング部門とのジョイント
日時:2005 年 1 月 22 日 9:00 – 17:45, 23 日 9:00 – 16:30
場所:名古屋大学東山キャンパス

3. 国際パネルディスカッション
Information at micro- and nanolevels is crucial in research on biomechanics
第 17 回日本機械学会バイオエンジニアリング部門とのジョイント
日時:2005 年 1 月 22 日 14:30 – 16:30
場所:名古屋大学東山キャンパス
Organizer & Chair: H. Wada (Tohoku Univ.)
Panelists: T. Murakami (Kyushu Univ.), K. Tanishita (Keio Univ.), H. Zao (The Univ. of Kentucky) and C. T. Lim (National Univ. of Singapore)

4. シンポジウム
マイクロ・ナノバイオメカニクス
第 44 回生体医工学大会とのジョイント
日時:2005 年 4 月 26 日 9:00 – 11:00
場所:つくば国際会議場
座長:谷下一夫(慶應義塾大学)
和田 仁(東北大学)
1. 機械刺激負荷に対する Ca^{2+} 応答の IP_3 依存性
牛田多加志, 佐野 稔, 岩吉俊輔, 古川克子(東京大学)
2. 軟骨組織・軟骨細胞の経時的圧縮変形挙動
村上輝夫, 坂井伸朗, 澤江義則, 岡本真季(九州大学)
3. 原子間力顕微鏡によるタンパク質モータの可視化
和田 仁(東北大学)
4. 培養骨芽細胞の局所変形負荷に対するカルシウムシグナル応答

佐藤克也[1)], 安達泰治[2)], 北條正樹[2)], 冨田佳宏[1)] 1)神戸大学, 2)京都大学

5. 培養内皮細胞の形態変化に及ぼすせん断応力と静水圧の相乗作用
大橋俊朗, 菅谷嘉晃, 坂元尚哉, 佐藤正明(東北大学)

6. 内皮細胞周辺の力学的特性が毛細血管ネットワーク形成に及ぼす影響
植田晃然[1)], 山村菜穂子[1)], 古賀理基[1)], 池田満里子[1)], 工藤 奨[2)], 谷下一夫[1)]
1)慶應義塾大学, 2)芝浦工業大学

7. イオンチャネルを介した血流センシング機構
安藤譲二, 山本希美子, 曽我部隆影(東京大学)

5. 発表

The 2nd Japan-Switzerland Workshop on Biomechanics
日時:2005 年 9 月 13 日 8:30 – 18:00, 15 日 8:30 – 18:00, 16 日 8:30 – 12:00
場所:京都ガーデンパレス

6. オーガナイズセッション

Special Symposium on "Biomechanics at micro- and nanoscale levels"
The second Asian Pacific Conference on Biomechanics とのジョイント
日時:2005 年 11 月 25 日
場所:Howard International House, Taipei
Organizer: H. Wada (Tohoku Univ.)
8:30 – 9:30 Cell mechanics
11:00 – 12:00 Cell response to mechanical stimulation
15:00 – 16:00 Tissue engineering
16:10 – 17:10 Computational biomechanics

7. オーガナイズセッション

マイクロ・ナノバイオメカニクス
第 18 回日本機械学会バイオエンジニアリング部門とのジョイント
日時:2006 年 1 月 13 日 9:30 – 12:15, 14 日 9:30 – 15:00
場所:新潟市朱鷺メッセ

8. オーガナイズセッション

International Workshop on Biomechanics and Tissue Engineering at Micro- and Nanoscale Levels
第 18 回日本機械学会バイオエンジニアリング部門とのジョイント
日時:2006 年 1 月 13 日 14:30 – 17:00
場所:新潟市朱鷺メッセ
Organizer & Chair: H. Wada (Tohoku Univ.)
14:30 – 15:00 Central role of cytoskeletal prestress in cell mechanics,
N. Wang (Harvard School of Public Health)
15:00 – 15:30 Chondrocyte deformation and mechanotransduction in cartilage model systems,
D. Bader (Queen Mary Univ. of London)
15:30 – 16:00 Functional tissue engineering for soft tissue repair: Matching in vivo biomechanics,
D. Butler (Univ. of Cincinnati)
16:00 – 16:30 Engineered Scaffold Architectures for Bone Regeneration,
S. J. Hollister (Univ. of Michigan)
16:30 – 17:00 Measurement of cochlear mechanical responses using laser interferometer,
T. Ren (Oregon Health & Science Univ.)

9. オーガナイズセッション
マイクロ・ナノバイオメカニクス:微小レベルで生体の力学挙動を知る
第 45 回生体医工学大会とのジョイント
日時:2006 年 5 月 15 日 9:00 – 10:30
場所:福岡国際会議場
オーガナイザ・座長:松本健郎(名古屋工業大学)
オーガナイザ・座長:宮崎 浩(大阪大学)
オーガナイザ:村上輝夫(九州大学)
1. マウス尾腱より摘出したコラーゲン原線維の力学的性質
山本憲隆, 杉浦和成(立命館大学)
2. 線維芽細胞の引張特性に対する微小管とアクチンフィラメントの寄与
宮崎 浩, 岡田健太(大阪大学)
3. 単一生細胞の力学的履歴効果
川端和重(北海道大学)
4. マイクロパターニング技術を用いた細胞の形状・配向制御ならびに力学応答解析
長山和亮[1)], 出水康仁[1)], 梅原徳次[2)], 松本健郎[1)] 1)名古屋工業大学, 2)名古屋大学
5. マウス卵子透明帯硬化による多精子受精拒否への影響
村山嘉延[1)], 鎌倉大和[1)], 笛田洋一[1)], 中村寛子[2)], 水野仁二[2)], 赤石一幸[2)], 乾 裕明[2)],
クリストス コンスタンチノウ[3)], 尾股定夫[1)]
1)日本大学, 2)乾マタニティクリニック, 3)スタンフォード大学
6. 赤血球流動のマルチスケールシミュレーション
和田成生, 北川義隆, 坪田健一, 山口隆美(東北大学)

10. Thread
5th World Congress of Biomechanics
日時:2006 年 7 月 29 日 – 8 月 4 日
場所:Munich, Germany
Thread 3: Biomechanics at micro- and nanoscale levels (Thread organizer: H. Wada)
1. Cell mechanics (Organizers: K. Tanishita & H. Wada)
2. Molecular biomechanics (Organizer: M. Sato)
3. Mechanobiology of micro- and nano-scale levels (Organizer: T. Ushida)
4. Computational biomechanics (Organizer: T. Yamaguchi)

11. オーガナイズセッション
マイクロ・ナノバイオメカニクス
日本機械学会年次大会バイオエンジニアリング部門とのジョイント
日時:2006 年 9 月 19 日 10:30 – 17:00
場所:熊本大学

12. オーガナイズセッション
マイクロ・ナノバイオメカニクス
第 19 回日本機械学会バイオエンジニアリング部門とのジョイント
日時:2007 年 1 月 7 日 9:30 – 16:00, 8 日 11:00 – 17:45
場所:仙台国際センター

13. オーガナイズセッション
International Workshop on Biomechanics and Tissue Engineering at Micro- and Nanoscale Levels
第 19 回日本機械学会バイオエンジニアリング部門とのジョイント

日時:2007 年 1 月 8 日 9:45 – 12:00
場所:仙台国際センター
Organizer & Chair: H. Wada (Tohoku Univ.)

9:45 – 10:30 The micro-structural strain response of tendon, H. R. C. Screen (Queen Mary Univ. of London)

10:30 – 11:15 Human hearing from a biomedical engineering point of view, S. Stenfelt (Linkoping Univ.)

11:15 – 12:00 Design of PIV experiments on collapsible-tube oscillation onset, to match numerical simulation, C. D. Bertram (Univ. of New South Wales)

14. 公開シンポジウム(研究者向け) Symposium on Biomechanics at Micro- and Nanoscale Levels
日時:2007 年 11 月 9 日(土) 9:30 - 17:10
会場:東京大学生産技術研究所 駒場リサーチキャンパス An 棟 2 階 コンベンションホール
Program

9:30–9:40 Introduction, Hiroshi Wada, Project Leader (Tohoku University)

9:40–10:00 Structural analysis of the motor protein prestin, Hiroshi Wada (Tohoku University)

10:00–10:20 Effects of cytoskeletal structures on elastic and viscoelastic properties of cells in soft tissues, Takeo Matsumoto (Nagoya Institute of Technology)

10:20–10:40 Biomechanical properties of collagen gel associated with microvessel formation in vitro, Kazuo Tanishita (Keio University)

10:40–11:00 Depth-dependent compressive behaviors of articular cartilage and chondrocytes, Teruo Murakami (Kyushu University)

11:10–11:30 Cytoskeletal reassembling and calcium signaling responses to mechanical perturbation in osteoblastic cells, Taiji Adachi (Kyoto University)

11:30–11:50 Experimental estimation of preexisting tension in single actin stress fiber of vascular cells, Masaaki Sato (Tohoku University)

11:50–12:10 Biophysical mechanisms of tension-dependent formation of stress fibers from actin meshwork, Masahiro Sokabe (Nagoya University)

13:30–14:00 Invited Lecture, Micro- and nanoscale biomechanics in Taiwan, Fong-Chin Su (National Cheng Kung University)

14:00–14:30 Invited Lecture, Biomechanics research advancement in Singapore, James Cho-Hong Goh (National University of Singapore)

14:40–15:00 Effects of cyclic hydrostatic pressure loading on regulation of chondrocyte phenotypes, Takashi Ushida (The University of Tokyo)

15:00–15:20 Effects of a shear flow and water filtration on the cell layer of a hybrid vascular graft, Takeshi Karino (Hokkaido University)

15:20–15:40 Tissue reconstructions for motor organs with mechanically structured grafts, Kazuo Takakuda (Tokyo Medical and Dental University)

15:50–16:10 Microscopic analysis of bone, Masao Tanaka (Osaka University)

16:10–16:30 Computational biomechanics of blood flow in cardiovascular diseases, Takami Yamaguchi (Tohoku University)

16:30–16:50 Microstructural mechanism of skeletal muscle injury and a new constitutive model of skeletal muscle, Eiichi Tanaka (Nagoya University)

16:50–17:10 Mechanical characteristics of vascular cells and tissues exposed to deformation, freezing, and shock waves: measurements and theoretical predictions, Hiroshi Yamada (Kyushu Institute of Technology)

15. 公開シンポジウム(一般向け)「マイクロ・ナノバイオメカニクスの開拓」
日時:2007 年 11 月 10 日 13:20 - 15:30
会場:東京大学生産技術研究所 駒場リサーチキャンパス An 棟 2 階 コンベンションホール
プログラム
13:20 - 13:30 紹介 代表者 和田仁(東北大学)
13:30 - 14:00 「生体のマイクロ・ナノ構造と細胞のメカニクス」 松本健郎(名古屋工業大学)
14:00 - 14:30 「力学刺激に対する生体マイクロ・ナノ構造の適応的応答」 安達泰治(京都大学)
14:30 - 15:00 「マイクロ・ナノバイオメカニクスの再生医療への応用を目指して」 牛田多加志(東京大学)
15:00 - 15:30 「生体マイクロ・ナノ構造とコンピュータモデリング」 田中正夫(大阪大学)

4．3．出版物

1. Biomechanics at Micro- and Nanoscale Levels, Introduction of the Project. Sanko Printing, 2004.
2. Biomechanics at Micro- and Nanoscale Levels, Vol. I. World Scientific Publishing, 2005. <http://www.worldscibooks.com/engineering/5704.html> [accessed December 17, 2007]
3. Biomechanics at Micro- and Nanoscale Levels, Vol. II. World Scientific Publishing, 2006. <http://www.worldscibooks.com/engineering/6082.html> [accessed December 17, 2007]
4. Biomechanics at Micro- and Nanoscale Levels, Vol. III. World Scientific Publishing, 2007. <http://www.worldscibooks.com/engineering/6520.html> [accessed December 17, 2007]
5. Biomechanics at Micro- and Nanoscale Levels, Vol. IV. World Scientific Publishing, 2007. <http://www.worldscibooks.com/engineering/6593.html> [accessed December 17, 2007]
6. Medical Bio. 4(6), (株)オーム社, 2007.
7. 日経サイエンス. 37(13), (株)日経サイエンス, 2007.
8. 生体医工学. 46(1), (社)日本生体医工学会, 2007.

5．研究成果による産業所有権の出願・取得状況

1. 産業財産権の名称・・・「血液浄化装置及び血液浄化方法」
   発明者名・・・磯上尚志, 田中哲也, 山口隆美
   産業財産権の種類・・・特許権
   番号・・・特開 2006-223723
   公開年月日・・・2006/8/31
   出願年月日・・・2005/2/21

2. 産業財産権の名称・・・「細胞把持・回転観察装置」
   発明者名・・・松本健郎, 大原大典, 長山和亮
   産業財産権の種類・・・特許権
   番号・・・特願 2008-43987
   出願年月日・・・2008/2/26

3. 産業財産権の名称・・・「生体内管腔体評価装置」
   発明者名・・・松本健郎, 長山和亮, 武澤健司, 益田博之
   産業財産権の種類・・・特許権
   番号・・・特願 2007-053508
   出願年月日・・・2007/3/5

6．研究の概要

生命現象の本質的な多様性は，遺伝子のみではなく，細胞をめぐるマイクロあるいはナノスケールの構造と遺伝情報との相互作用によって担われており，その中でも，力学的相互作用の意義は極めて大きい．従って，力学的環境と生命機能の関係を解明することができれば，細胞及び組織の構造と機能をコントロールする手段を見いだせる可能性が高い．そこで，以下の4研究項目を設定した．

研究項目 A01「生体マイクロ・ナノ構造のメカニクス」の研究

生体を構成する細胞や生体分子は力学的な環境に絶えずさらされており，細胞の形態や機能を環境に対して最適に維持している．その機構を理解するには力学原理を中心としたバイオメカニクス的考え方が重要である．そこで本研究では，細胞レベルのマクロな視点から細胞や組織の力学現象を明らかにすると共に，生体分子レベルのナノの視点から細胞内構成物や組織構成物の力学現象を明らかにする．

研究項目 A02「力学刺激に対する生体マイクロ・ナノ構造の応答」の研究

力学的刺激に対して応答を示す細胞において，細胞骨格等の内部構造や細胞外マトリクスとの接着部位が，メカノセンサーとしての役割を果たしていると考えられるが，その詳細な機構は不明である．そこで本研究では，引張・圧縮・せん断等の種々の力学的刺激の下，どのような機構により細胞骨格や接着斑が再構築され，メカノセンサーとしての機能が調節されるかについて，マイクロ・ナノレベルのバイオメカニクスの視点で明らかにする．

研究項目 A03「生体マイクロ・ナノ構造制御による組織創製」の研究

生体細胞と足場材料を組み合わせたいわゆるティッシュエンジニアリングが盛んに研究されているが，細胞や生体分子が生体内において機能発現をする環境を考えると，力学的要因を無視することはできない．そこで本研究では，力学的環境を制御することによって目的とする機能発現をする細胞を誘導し，最終的には血管，腱・靭帯，軟骨，骨，歯，歯根膜などの組織創製を行う技術を開発する．

研究項目 A04「生体マイクロ・ナノ構造とバイオインフォマティクス」の研究

従来の「バイオインフォマティクス」研究では，生命体内部の複雑な力学的環境を考慮に入れない分子動力学的解析などが主流となっており，生命体の統合的理解に結びつけることが困難になっている．そこで本研究では，生体の構成諸単位（低分子，高分子，細胞小器官，細胞など）の複雑な相互作用のシステムを厳密な力学モデルとして再構成し，生命現象を再現する計算バイオメカニクスの構築をはかる．

7．研究成果の要点および将来展望

本研究成果をまとめたものを図1に示す．生体にとって力学的刺激は生化学的刺激に勝るとも劣らず重要である．そこで，本研究では，細胞及び組織レベルで力が作用した際の応力及び歪を定量的に計測し，また，その応力や歪をセンシングするメカニズムを明らかにすることにより，サイエンスとしてバイオメカニクスの基礎を確立した．そして，その知見を関節軟骨，繊維，肝臓の組織などの再生に応用した．

研究各項目では，

1. 研究項目 A01「生体マイクロ・ナノ構造のメカニクス」では，細胞と細胞内構造，細胞間及び細胞と周囲組織との力学的相互関係を定量的に明らかにした．
2. 研究項目 A02「力学的刺激に対するマイクロ・ナノ構造の応答」では，細胞の機械刺激受容／応答機構におけるMSチャネルの活性化機構，および細胞骨格の役割を明らかにした．
3. 研究項目 A03「生体マイクロ・ナノ構造制御による組織創製」では，力学的環境を整え，関節軟骨，人工骨・歯根と繊維組織結合部位及び肝臓の組織を再構築し，また，ハイブリッド人工血管を開発した．

4. 研究項目A04「生体マイクロ・ナノ構造とバイオインフォマティクス」では，骨のマイクロ構造変化，動脈硬化・癌の発生メカニズム，骨格筋及び細胞の損傷特性を数値計算により明らかにした．

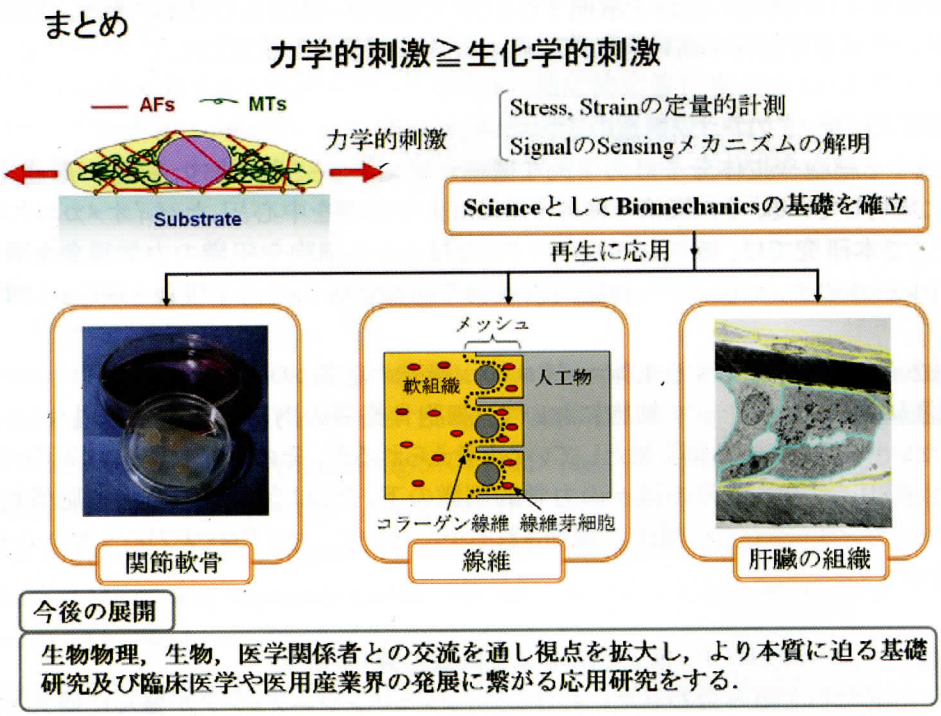

図 1．本研究成果のまとめ．

バイオメカニクスの今後の展開として以下を考えている．

1. 力学を基礎とし，
   a. 生体システムの構造・機能を定量的計測，モデル化する手法を開発する．
   b. 複雑な生体現象の基礎的メカニズムの解明とその統合化によるシステムの評価法を開発する．
2. 生物物理，生物，医学関係者との交流を通じ視野を拡大し，
   a. 生体現象の本質に迫る基礎研究を行う．
   b. 臨床医学や医用産業界の発展に繋がる応用研究をする．

また，上述の目的達成のために，研究会の設立や学会の発足を目指す．

研究項目 A01

生体マイクロ・ナノ構造のメカニクス

CELL MECHANICS