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1 BACKGROUND AND PERSPECTIVES

Background

The Maurice E. Müller Institute for Biomechanics (MIB) was established as a joint venture between the Maurice E. Müller Foundation and the Medical Faculty of the University of Bern when Prof. M.E. Müller retired (in 1981) as Chairman of the Department of Orthopaedic Surgery at the Inselspital. The MIB attained legal status as a full University Institute on 1. January 1995, this decision having been reached by the Bernese Government in May 1994 and endorsed by the State the following month. The objectives of the MIB are to conduct basic and applied biomechanical research of the locomotor system at the physiological, tissue, cellular and molecular levels. It is supported by a basic operation grant from the Maurice E. Müller Foundation, by funds from the University of Bern, by a grant from the AO/ASIF Foundation and by project grants from the Swiss National Science Foundation, as well as from various other foundations and industrial sources. The MIB is currently under the Directorship of Prof. Ernst B. Hunziker, who was elected to this position by the Bernese Government in the autumn of 1989.

Objectives

The MIB's efforts are directed towards forging an integrated understanding of the structure and function of the musculoskeletal system at the physiological, tissue, cellular and molecular levels, and of developing and optimizing information, materials and techniques for the clinical detection and treatment of musculoskeletal diseases. It is thus conceived as a link between academic research, surgical practice and industrial development. Active collaborations with several research institutes at Bern and other universities, with the Department for Orthopaedic Surgery at the Inselspital and with the AO/ASIF Foundation's Research Institute in Davos, as well as with industrial partners, play an important part in building up the larger and more objective picture of the musculoskeletal system as a whole.

Previous and Current General Research Program

From the time of its foundation in 1981 until 1988, the MIB was directed by Prof. Stephan S. Perren. Its goals during this period were to study the normal and disturbed loading patterns of the locomotor apparatus, to advance our understanding of this system and to profit therefrom by improving the principles, techniques, instrumentation and implants applied in orthopaedic surgery. When Prof. Ernst B. Hunziker took over the Directorship in 1989, he broadened the MIB’s scope of research activities to include basic and applied aspects of skeletal tissue biology, from the physiological down to the molecular level.

Improvements in microstructural preservation, morphometric analyses at the histological level, the biocompatibility of implant materials, interfacial (adhesion) biology, and the micro mechanical properties of skeletal tissues, as well as their responses to mechanical stimuli at the tissue, cell and molecular levels, represent but a few of the directions followed. Research activities in the field of classical biomechanics are under the supervision of Prof. Lutz-P. Nolte, who has extended the MIB's research activities in this area to include computer-assisted surgery. In 1993, Dr. Nolte was appointed Head of the MIB's Division of Orthopaedic Biomechanics. In addition to being its Director, Prof. Hunziker is also Head of the MIB's Division of Biology, Prof Dr. Beat Trueb being its Associate Head.

With these new dimensions, the MIB is now in a better position to tackle questions raised in connection with the biomechanics of the musculoskeletal system, prostheses, endoprostheses, fracture treatment and novel biologically-based treatment strategies.

Organization

The Institute is comprised of a staff of about 65 people, including graduate students, medical scientists, biologists, engineers, computer specialists, technicians and research fellows. It consists of two divisions, with a central unit for administration and maintenance. The research activities of one division relate to orthopaedic biomechanics and surgical techniques, whilst those of the other pertain to basic and applied biological aspects of the musculoskeletal apparatus. The two divisions collaborate with one another and are supported by a basic technical staff furnishing histological, computer, mechanical and electronic services. Further information relating to the MIB is available on the Internet @ http://www.mem.unibe.ch.

Significance of Research Program

Research activities conducted at the MIB are contributing to our basic understanding of the structure and function of the musculoskeletal system and of their controlling mechanisms at the physiological, tissue, cellular and molecular levels. Knowledge thus gained will help us to further develop and optimize materials for clinical application, to conceive novel biologically based treatment strategies and to follow a more rational, scientific approach to the treatment of diseases of the musculoskeletal system.

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2 RESEARCH ACTIVITIES

2.1. Division of Biology

2.1.1 Molecular Biomechanics

Activities in this research area are directed towards elucidating the composition and functional properties of skeletal tissue elements at the molecular level. Experimental methodology involves principally in-vitro systems - cartilage and skeletal connective tissues being the main tissues investigated. Current topics dealt with include an analysis of the structural and functional properties of components contained within adult human articular cartilage, foetal cartilages and connective tissues. Newly-identified constituents of the extracellular matrix are being cloned, sequenced and analyzed from a functional viewpoint.

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Analysis of the α-Actinin/Zyxin Interaction
Li B. and Trueb B.

The yeast two-hybrid system was used to search for interaction partners of the focal adhesion protein zyxin. Screening of two different cDNA libraries, one prepared from human placenta, the other from human heart, yielded several positive clones that occurred in both searches, including clones coding for cyclophilin, nebulette and α-actinin. The zyxin/α-actinin interaction was analyzed in detail. By site-directed mutagenesis, a linear motif of 6 amino acids (Phe-Gly-Pro-Val-Val-Ala) present at the N-terminus of zyxin was found to play a critical role. Replacement of a single amino acid within this motif abolished binding to α-actinin in blot overlays as well as in living cells. On the other hand, the interaction site in α-actinin was mapped to a conformational determinant present in the center of the protein as demonstrated by a fragment deletion analysis. This binding site involved a tandem array of two complete spectrin-like domains. Only fragments that were able to dimerize in yeast also bound to zyxin, suggesting that dimerization of α-actinin is essential for zyxin binding.

Mechanical Stress Is Required for High-Level Expression of Connective Tissue Growth Factor
Schild C. and Trueb B.

We have used the gene array technology to analyze differences in gene expression between mechanically stressed and relaxed fibroblasts. A number of stress-responsive genes were identified that showed a 2-6 fold difference in their relative expression. Connective tissue growth factor CTGF was among those

genes that showed the most striking up-regulation by mechanical stress. Its regulation occurred at the transcriptional level and was reversible. A new steady state level of the CTGF mRNA was reached within less than 6 h after stress relaxation. Mechanical stress was absolutely required for sustained high level expression; TGF-β which is also known to stimulate CTGF synthesis was not sufficient on its own. Experiments with specific inhibitors suggested that a protein kinase and a tyrosine phosphatase were involved in the transduction of the mechanical stimulus to gene expression. Since CTGF controls the synthesis of several extracellular matrix proteins, it is likely that this growth factor is responsible for the increased synthesis of collagen I and other matrix proteins in stressed fibroblasts.

A Novel, FGF Receptor-Like Protein Is Involved in the Formation of the Skeleton
Wiedemann M. and Trueb B.

We have recently discovered a novel protein that is specifically expressed in human cartilage. This protein represents a transmembrane protein and resembles the members of the FGF receptor family. Here, we have characterized the homologous protein (termed Fgfrl1) from mice. Fgfrl1 contains three extracellular Ig C2 loops and an acidic box. These domains share 29-33% sequence identity (48-50% similarity) with FGF receptors 1-4. The intracellular portion of the novel protein, however, is not related to the FGF receptors. It lacks the tyrosine kinase domain that would be required for signal transduction by transphosphorylation. It is therefore likely that Fgfrl1 functions as a pseudoreceptor, which interacts with FGF ligands, but does not transduce the signal to the interior of the cells. The murine gene for Fgfrl1 comprises 6 exons and is located on mouse chromosome 5 in close proximity to the Idua gene for L-iduronidase. We speculate that the novel protein is involved in the modulation of FGF signaling during endochondral ossification.

2.1.2 Cellular Biomechanics

Research activities in this area are concerned with elucidating the mechanisms whereby fibroblasts within highly tensile-stressed tissues i.e., the skin, ligaments and tendons, remodel their extracellular matrix in response to variable forces. The goal is to understand how these cells sense the mechanical signals and transform them into a specific biosynthetic response. Several matrix proteins have recently been identified whose rates of synthesis correlate with the degree of tensile stress to which the cells are exposed. In order to assess the effects of these proteins on gene transcription, fibroblasts are cultured on elastic substrates and subjected to controlled strain. Such knowledge should help us to devise the means of manipulating not only the quantity but also the composition (and hence the mechanical properties) of repair tissue formed in response to injury.

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The Control of Tenascin-C Expression by Equi-Biaxial Strain in Fibroblasts
Chiquet M., Sarasa-Renedo A. and Tunç-Civelek V.

We have constructed a device for applying cyclic, equi-biaxial strain to fibroblasts cultured in multiwell dishes on fibronectin-coated silicon elastomer membranes (see last year's report). Using this machine, we are studying the mechanisms regulating the expression of tenascin-C, an extracellular matrix protein known to be induced by mechanical stress both in vitro (Trächslin et al., *Exp. Cell Res.* 247: 320-328) and in vivo (Flück et al., *J. Cell Sci.* 113: 3583-3591). Tenascin-C mRNA was found to be up-regulated several fold by applying cyclic (0.3 Hz) strain (15%) to chick embryo fibroblasts for 6 hours. Mechanical stressing of cells in the presence of cycloheximide led to a superinduction of tenascin-C mRNA, indicating that no new protein synthesis is required for this response. The increase in tenascin-C mRNA levels after applying cyclic strain was suppressed by the broad range proteine kinase inhibitors genistein and staurosporin; however PD98059, a specific inhibitor of MAP kinase ERK-1/2 phosphorylation, had no effect. Partial inhibition of the response by gadolinium chloride points to a possible involvement of stretch-sensitive ion channels. Interestingly, Y27632 which selectively inhibits Rho-dependent protein kinase (ROCK), almost completely blocked cyclic strain-dependent induction of tenascin-C mRNA in fibroblasts. This indicates that cytoskeletal tension regulated by ROCK is required for the mechanotransduction events that lead to increased tenascin-C expression. In contrast to a report on tenascin-C mRNA induction by cyclic stretch in rat cardiomyocytes (Yamamoto et al., *J. Biol. Chem*. 274: 21840-46, 1999), we found that this response in chick fibroblasts was not inhibited by the radical scavenger N-acetyl cysteine. This argues against an involvement of reactive oxygen species in the mechanotransduction mechanism in our case. In addition to exploring the signaling cascades involved in mechanical stimulation, we currently investigate the control of tenascin-C expression by cyclic mechanical stress at the gene promoter level, focussing on putative mechano-responsive enhancer sequences.

Tensile Stress-Dependent Expression of Collagen XII and Fibronectin in Fibroblasts: Evidence for Distinct Signaling Pathways
Flück M., Tunç-Civelek V. and Chiquet M.

Mechanical loading is important for tissue remodeling and increased extracellular matrix deposition, yet the intracellular mechanisms controlling production of distinct matrix proteins in response to mechanical stimuli are not known in detail. By culturing fibroblasts on collagen type-I gels under either stressed or relaxed conditions, we analyzed the requirements for tensile stress-induced expression of fibronectin and collagen XII, respectively. Collagen XII is

induced more rapidly than fibronectin in stretched collagen gels. Inhibition experiments indicate that integrins, tyrosine kinases and PKC are involved in tensile stress-dependent production of the two matrix proteins by fibroblasts, however in distinct ways. Chronic exposure to the tyrosine phosphatase inhibitor orthovanadate blocked increased production of both fibronectin and collagen XII by cells under tension. The protein tyrosine kinase inhibitor genistein partially inhibited tensile stress-induced accumulation of collagen XII but not fibronectin, whereas an inhibitor of MAP kinase ERK-1/2 phosphorylation, PD98059, showed the reverse effect. Stress-dependent production of both proteins was partially inhibited by the protein kinase C inhibitors bisindoylmaleimide and calphostin C. In contrast, staurosporine as well as pretreatment with phorbolester specifically blocked collagen XII but not fibronectin accumulation in mechanically stressed fibroblasts. Similarly, anti-α5 and -β1 integrin antibodies specifically inhibited stress-dependent collagen XII but not fibronectin accumulation. However, no correlation was found between protein/phosphorylation levels of focal adhesion kinase and collagen XII production. β1-Integrins, a tyrosine kinase other than FAK, and a distinct PKC appear selectively required for increased production of collagen XII in mechanically stressed cells, whereas ERK-1/2 signaling is necessary for fibronectin but not collagen XII induction.

Mechanical Properties of Collagen I Gels Reconstituted in the Presence of Other Exracellular Matrix Proteins

Huber F., Schalet B. and Chiquet M.

In response to mechanical stimulation, connective tissue cells increase the expression levels of several collagen I associated proteins. Among these are tenascin-C and collagen XII, which might alter the mechanical properties of the extracellular matrix by crosslinking and stiffening the fibrillar collagen I lattice. To test this hypothesis, we use a modified isometric force monitoring apparatus (Kolodney and Wysolmerski, 1992 JCB 117:73-82). A native fibrillar collagen I gel is assembled between two polythylene holders. One of the holders is attached to a strain gauge and the other to a displacement actuator. Forces can be applied to the collagen I gel my moving the actuator. The experiments involve reconstituting collagen I gels in the presence of varying amounts of collagen XII, tenascin-C, fibronectin, or serum albumin as a control. The gels are stretched by moving the actuator in small steps and equilibrium forces are monitored. From the resulting curves, the Young modulus can be calculated which is a measure for the stiffness of the material. Preliminary results support our hypothesis that co-assembly with other extracellular matrix proteins changes the mechanical properties of a collagen I matrix.

2.1.3 Tissue Biomechanics

Research in this area is directed towards understanding the structural-functional relationships pertaining in skeletal connective tissues, i.e., in cartilage, bone, ligaments and tendons. Emphasis is being placed on the role not only of physiological, but also of non-physiological, mechanical loading during musculoskeletal development, remodelling, disease and injury. Methodologies employed include the stereological and histological characterization of tissue microstructure, molecular and biochemical assaying of connective tissue metabolism, and the measurement of tissue biophysical properties. These projects are being undertaken with a view to improving our understanding of the aetiology of diseases such as osteoarthritis and to developing new therapeutic strategies for their treatment.

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Compressive Properties of Semi-IPN Hydrogels are Comparable to Cartilage Tissue

Goodwin K., Wong M., Lydon F. and Tighe B.

The transplantation of tissue-engineered constructs is a promising treatment to repair cartilage defects. However, there is a large clinical need for mechanically stronger constructs since the majority of scaffold materials (eg. alginate) used for defect repair have relatively poor compressive properties when compared to those of normal articular cartilage. This mismatch in mechanical properties between the repair transplant and the native tissue reduces the ability of the construct to withstand the rigorous loading demands placed on the tissue *in vivo*. The goal of this work is to find an alternative cartilage scaffold material for tissue repair with mechanical properties that approach those of native cartilage tissue. One group of biomaterials that offers a mechanically stronger alternative to scaffold materials currently in use are semi-interpenetrating network (semi-IPN) hydrogels. In this study we have tested three different hydrogel samples to compare the static and dynamic compressive properties of these materials to cartilage tissue and alginate**.** The equilibrium modulus (EqM) of the cartilage samples was 0.8 ± 0.1 MPa. The hydrogel samples had comparable equilibrium moduli, with Hydrogel 2 showing no significant difference from cartilage ($p=0.055$). All three hydrogel samples had an equilibrium modulus significantly greater than that of alginate (0.03 ± 0.005 MPa). The response of the hydrogels to sinusoidal dynamic compression showed dynamic modulus values ranging from 4.5 ± 1.2 (Hydrogel 2) to 26.2 ± 1.9 MPa (Hydrogel 3) at a frequency of 0.0025 Hz and from 6.1 ± 1.7 (Hydrogel 2) to 46.6 ± 5.6 MPa (Hydrogel 3) at a frequency of 0.833 Hz. In comparison, the dynamic modulus of articular cartilage was 7.5 ± 1.3 and 15.4 ± 2.1 MPa at frequencies of 0.0025 and 0.833 Hz respectively. Hydrogel 1 most closely approximated the dynamic modulus of cartilage, but the dynamic modulus values were all significantly different between the two samples except at a frequency of 0.0025Hz ($p=0.011$). This study investigated the mechanical properties of semi-interpenetrating network hydrogels for use as a potential cartilage scaffold material for defect repair.

Novel Collagenase-Sensitive Poly-(Ethylene Glycol) Based Hydrogels for Cartilage Repair

Park Y., Luetolf M., Hubbell J., Hunziker E.B. and Wong M.

Cartilage is one of the important targets for tissue engineering because it does not regenerate in partial thickness defects. Here we report the on the development of a novel, collagenase-sensitive poly-(ethylene glycol) (PEG) based hydrogel for use as a cartilage scaffold. The properties of this class of hydrogel can be easily modified and can be applied directly to the wound site in liquid form where it polymerizes *in situ*. The hydrogel used in this study has the distinguishing feature in that a collagenase-sensitive peptide was used as a cross-linker for gelation. In this study, the mechanical properties of the hydrogel (elastic modulus and swelling ratio) were measured. Chondrocytes were cultured inside the

hydrogel up to one month to determine the morphology and viability of the cells. The elastic modulus of the 8 arm PEG was about 2.8 times higher than that of the 4 arm PEG. Also, swelling ratio of the 8 arm PEG is around 2 times lower than that of the 4 arm PEG. The hydrogels do not cause cytotoxicity even after a one month culture period. Cells aquired a fibroblastic shape only in the 4 arm, collagenase-sensitive hydrogel, whereas cells in other hydrogels showed a rounded morphology. Because the 8 arm, collagenase-sensitive PEG hydrogel can be remodeled by cellular enzymes and doesn't induce the dedifferentiation of chondrocytes during culture, this material has the greatest promise as a cartilage scaffold.

Collagen Fibrillogenesis by Chondrocytes in Alginate
Wong M., Siegrist M., Gaschen V., Park Y., Hunziker E.B. and Studer D.

Collagen is the primary structural component in connective tissue. The poor mechanical properties of most cell-seeded cartilage grafts used for cartilage repair can be attributed to the low level of collagen synthesized compared to native cartilage. In this study, the synthesis and assembly of collagen by chondrocytes in hydrogels was investigated, paying particular attention to the role crosslink formation in this process. Primary bovine chondrocytes were seeded in alginate and collagen synthesis assessed in the presence and absence of beta-aminopropronitrile (BAPN), a potent inhibitor of the enzyme lysyl oxidase and collagen crosslink formation. Cultures at day 21, 35 and 49 were evaluated using stereology, biochemistry and real-time RT-PCR. All measures of collagen synthesis (except hydroxyproline) significantly increased in the presence of 0.25 mM BAPN. By 35 days of culture, the average collagen fibril diameter was 62$\pm$10nm in control cultures and 109$\pm$20nm with BAPN supplementation. The collagen volume density increased from 5$\pm$3% in control cultures to 17$\pm$1% in the presence of BAPN. Likewise, the expression of cartilage specific collagens (type II and XI) and aggrecan increased significantly as a result of BAPN culture. These findings demonstrate the prominent role of collagen crosslinking in collagen fibrillogenesis and suggest approaches by which collagen synthesis and assembly could be controlled in tissue-engineered constructs.

Hydrostatic Pressure, Tension and Unconfined Compression Differentially Regulate Expression of Cartilage Matrix Proteins
Wong M., Siegrist M., Goodwin D. and Park Y.

Cartilage maturation follows a series of stages including proliferation, hypertropy, matrix calcification, apoptosis and replacement by endochondral bone. Continuum models of skeletal development suggest that this progression of cellular events may be arrested by cyclic hydrostatic pressure and accelerated by cyclic shear (or tension). Comprehensive molecular level studies to test these hypotheses, however, are lacking. The goal of this study was to expose the same population of chondrocytes to cyclic hydrostatic pressure, cyclic tension and

cyclic unconfined compression and to assess changes in the expression levels of cartilage matrix genes as a result of loading. Primary chondrocytes were isolated from calf bovine humeral head cartilage using a sequential pronase/collagenase digestion. The chondrocyte/2% alginate solution containing $4x10^6$cells/ml was polymerized in cylinders for hydrostatic pressure and unconfined compression and rectangular beams for tensile experiments. The gels were cultured for three days and subjected to three additional days of hydrostatic pressure, tension, or unconfined compression. After loading, total RNA was extracted from the samples and expression of extracellular matrix proteins was evaluated using RT-PCR. Each of the three loading modes was associated with a unique pattern of cartilage matrix gene expression. Hydrostatic pressure upregulated the expression of all cartilage matrix genes evaluated. Cyclic tension upregulated the message for type X collagen (1.8 fold) and aggrecan (1.6 fold). Cyclic unconfined compression was associated solely with the upregulation of cartilage oligomeric matrix protein (COMP). The expression of the cartilage-specific transcription factor SOX9 was also found to be sensitive to certain types of mechanical loading. Its expression increased 1.3 fold with hydrostatic pressure and 1.2 fold with tensile loading. We have demonstrated that the identical population of cells can dramatically alter its gene expression pattern based on the type of mechanical loading stimulus which is applied. The increase in the expression of matrix proteins with cyclic hydrostatic pressure is consistent with the hypothesis that hydrostatic pressure functions in the joint to arrest the maturational process leading towards endochondral ossification. Our finding of a 1.8 fold upregulation of type X collagen mRNA with cyclic tension is consistent with the view that tension or shear accelerates chondocyte maturation.

2.1.4 Microbiomechanics and Structural Biology

The main activities in this research area are directed towards elucidating the structural characteristics of skeletal tissues, particularly of cartilage and bone, and their functional correlates, using both *in vitro* and *in vivo* systems. Current topics include analysis of the mechanical properties and structural composition/organisation of growth- and articular cartilages and tendons, as well as investigations relating to the basic physiological mechanisms underlying the differentiation and activity regulation in these tissues.

With respect to bone tissue, studies pertain to mechanisms of osseoinduction and tissue integration processes (particularly as regards to implant materials). These projects are being undertaken with a view to developing new strategies for the treatment of traumatized or diseased cartilage and bone tissue.

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Functional Barrier Principle for Growth-Factor-Based Articular Cartilage Repair
Hunziker E.B. and Driesang I.M.K.

Induction of growth-factor-based repair in full-thickness articular cartilage defects can be impaired by the upgrowth of blood vessels and new bone into the cartilage compartment. By inserting a cell-excluding membrane (structural barrier) at the presumptive cartilage-bone interface, these unwanted effects can be prevented. However, placement of the membrane precisely at the said junction and its cell-tight sealing at the defect edges pose difficulties. In the present study, we postulated that if an anti-angiogenic factor (Suramin) was included within the chondrogenic growth factor/matrix construct applied to the cartilaginous compartment of the defect void, the consequent inhibition of vascular upgrowth would, as a matter of course, prevent the upgrowth of osseous tissue into this region (functional barrier principle). The desired effect was indeed achieved, reconfirming that osteogenic activity cannot take place in the absence of a blood vasculature. The surgical procedure could be performed precisely and reproducibly.

Quantitative Structural Organization of Normal Adult Human Articular Cartilage
Hunziker E.B., Quinn T.M. and Häuselmann H.J.

Objective: Data pertaining to the quantitative structural features and organization of normal articular cartilage are of great importance in understanding its biomechanical properties and in attempting to establish this tissue's counterpart by engineering *in vitro*. A comprehensive set of such baseline data is, however, not available for humans. It was the purpose of the present study to furnish the necessary information.
Design: The articular cartilage layer covering the medial femoral condyle of deceased persons aged between 23 and 49 years was chosen for the morphometric analysis of cell parameters using confocal microscopy in conjunction with unbiased stereological methods. The heights of individual articular cartilage zones as well as those of the calcified cartilage layer and the subchondral bone plate were likewise quantified.
Results: The mean height of the hyaline articular cartilage layer was found to be 2.4 mm, the volume density of chondrocytes therein being 1.65%, the number of cells per mm^3 of tissue 9'626 and the mean cell diameter 13 µm. Other estimators (including matrix mass per cell and cell profile density) were also determined.
Conclusions: A comparison of these normal human quantitative data with those published for experimental animals commonly used in orthopaedic research reveal substantial differences, consideration of which in tissue engineering strategies destined for human application are of paramount importance for successful repair.

Mice With a Targeted Deletion of the Tetranectin Gene Exhibit a Spinal Deformity

Iba K., Durkin M.E., Johnsen L., Hunziker E.B., Damgaard-Pedersen K., Zhang H., Engvall E., Albrechtsen R. and Wever U.M.

Tetranectin is plasminogen-binding, homotrimeric protein belonging to the C-type lectin family of proteins. Tetranectin has been suggested to play a role in tissue remodelling, due to its ability to stimulate plasminogen activation and its expression in developing tissues such as developing bone and muscle. To test the functional role of tetranectin directly, we have generated mice with a targeted disruption of the gene. We report that the tetranectin-deficient mice exhibit a type of spinal deformity known as kyphosis, which is characterized by an increased curvature of the thoracic spine. The kyphotic angles were measured on radiographs. In 6 month old normal mice (n=27) the thoracic angle was $73^{o} \pm 2^{o}$, while in tetranectin-deficient 6 month old mice (n=35) it was $93^{o} \pm 2^{o}$ ($p < 0.0001$). In approximately one third of the mutant mice, X-ray analysis revealed structural changes in the morphology of the vertebrae. Histological analysis of the spines of tetranectin-deficient mice revealed an apparently asymmetric development of the intervertebral discs and an asymmetric activity of the growth plate of the vertebrae. In the most advanced cases, the growth plates appeared disorganized and irregular, with the disk material protruding through the growth plate. Tetranectin-null mice had a normal peak bone mass density and were not more suceptible to ovariectomy-induced osteoporosis than their littermates as determined by dual emission X-ray absorptiometry (DEXA) scanning. The tetranectin-deficient mouse may provide a model for human kyphotic disorders such as Scheuermann's disease.

Proteins Incorporated into Biomimetically-Prepared Calcium Phosphate Coatings Modulate their Mechanical Strength and Dissolution Rate

Liu Y., Hunziker E.B., Randall N.X., de Groot K. and Layrolle P.

In a previous investigation, we demonstrated that when bovine serum albumin (BSA) is biomimetically co-precipitated with Ca2+ and PO43- ions upon titanium alloy implants, it becomes incorporated into the crystal lattice and is not merely deposited on its surface. Moreover, the coating elicited a change in crystal structure from an octacalcium phosphate type to a carbonated apatite one, which bears a closer resemblance to natural bone mineral. In the present study, we investigated the dissolution rate and mechanical strength of such BSA-containing coatings as a function of protein concentration within the bathing medium (10 ng/ml to 1.0 mg/ml). BSA-containing coatings released Ca2+ ions more slowly (5 ppm/minute) than did non- BSA-containing ones (10 ppm/minute), but this rate did not change as a function of protein concentration within the bathing medium. In contrast, the strength of coatings increased almost linearly as a function of protein concentration within the bathing medium,

indicating that BSA incorporated into the crystal lattice enhances its mechanical strength in a concentration – dependent manner.

Ultrastructural cartilage abnormalities in MIA/CD-RAP-deficient mice

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MIA/CD-RAP is a small, soluble protein secreted from malignant melanoma cells and from chondrocytes. Recent evidence has identified MIA/CD-RAP as the prototype of a small family of extracellular proteins adopting an SH3 domain-like fold. It is thought that interaction between MIA/CD-RAP and specific epitopes in extracellular matrix proteins regulates the attachment of tumor cells and chondrocytes. In order to study the consequences of MIA/CD-RAP deficiency in vivo, we generated mice with a targeted gene disruption. The complete absence of MIA/CD-RAP mRNA and protein expression was demonstrated by reverse transcriptase, Western blot analysis, and enzyme-linked immunosorbent assay measurements of whole-embryo extracts. MIA(-/-) mice were viable and developed normally, and histological examination of the organs by means of light microscopy revealed no major abnormalities. In contrast, electron microscopic studies of cartilage composition revealed subtle defects in collagen fiber density, diameter, and arrangement, as well as changes in the number and morphology of chondrocytic microvilli. Taken together, our data indicate that MIA/CD-RAP is essentially required for formation of the highly ordered ultrastructural fiber architecture in cartilage and may have a role in regulating chondrocyte matrix interactions.

Proteoglycan Deposition Around Chondrocytes in Agarose Culture
Quinn T.M., Schmid P., Hunziker E.B. and Grodzinsky A.J

With a view towards the development of methods for cartilage tissue engineering, matrix deposition around individual chondrocytes was studied during de novo matrix synthesis in agarose suspension culture. At a range of times in culture from 2 days to 1 month (long enough for cartilage-like material properties to begin to emerge), pericellular distributions of proteoglycan and matrix protein deposition were measured by quantitative autoradiography, while matrix accumulation and cell volumes were estimated by stereological methods. Consistent with previous work, tissue-average rates of matrix synthesis generally decreased asymptotically with time in culture, as de novo matrix accumulated. Cell-scale analysis revealed that this evolution was accompanied by a transition from predominantly pericellular matrix (within a few μm from the cell membrane) deposition early in culture towards proteoglycan and protein deposition patterns more similar to those observed in cartilage explants at later times. This finding may suggest a differential recruitment of different proteoglycan metabolic pools as matrix assembly progresses. Cell volumes increased with time in culture, suggestive of alterations in volume regulatory processes associated with changes in the microphysical environment. Results emphasize a pattern of de novo matrix construction which proceeds outward from the pericellular matrix in a progressive fashion. These findings provide cell-scale insight into the mechanisms of assembly of matrix proteins and proteoglycans in de novo matrix, and may aid in the development of tissue engineering methods for cartilage repair.

A New Approach for Cryofixation by High-Pressure Freezing
Studer D., Graber W., Al-Amoudi A. and Eggli P.

A newly designed high-pressure freezing machine for cryofixation was established and tested (Leica EMPACT), based on ideas originally proposed by Moor and Riehle (1968). The new machine, essentially an improved version of our prototype, pressurizes the sample to 2000bar in a small containment (using methylcyclohexane as hydraulic fluid) and at the same time cools the containment at its outer surface by a jet of liquid nitrogen. The advantage of this approach is that the machine uses little liquid nitrogen and can be built small and light. The machine is able to vitrify and freeze well a variety of specimens, as for example plant leaves, yeast cells, liver or nerve tissue (some samples are shown on the Internet: http://www.ana.unibe.ch/empact). Cooling efficiency is the same as in the traditional machines that use liquid nitrogen to pressurize and simultaneously cool down the sample.

COMP Deficient Mice Have a Normal Skeletal Development
Svensson L., Aszodi A., Heinegard D., Hunziker E.B., Reinholt F.P., Fässler R. and Oldberg A.

COMP (cartilage oligomeric matrix protein) belongs to the thrombospondin gene family and is a homopentamer primarily expressed in cartilage. Mutations in the COMP gene result in the autosomal dominant chondrodysplasias pseudoachondroplasia (PSACH) and some types of multiple epiphyseal dysplasia (MED), which are characterized by mild to severe short-limb dwarfism and early-onset osteoarthritis. We have generated COMP-null mice to study the role of COMP *in vivo*. These mice show no anatomical, histological or ultrastructural abnormalities, and show none of the clinical signs of PSACH or MED. Northern blot analysis and immunohistohemical analysis of cartilage indicate that the lack of COMP is not compensated by any other member of the thrombospondin family. The results also show that the phenotype in PSACH/MED cartilage disorders is not caused by the reduced amount of COMP.

The Somatostatin Analogue Octreotide Inhibits Growth Hormone- but not Insulin-Like Growth Factor I-Stimulated Bone Growth in Hypophysectomized Rats

Zapf J., Gosteli-Peter M., Weckbecker G., Hunziker E.B. and Reinecke M.

Insulin-like growth factor (IGF) I mediates growth-promoting actions of growth hormone (GH). In the present study we investigated whether the somatostatin analogue octreotide blunts the stimulatory effects of GH and/or IGF-I on bone growth in hypophysectomized rats infused for 6 days with vehicle, GH or IGF-I. We found that octreotide significantly suppressed the GH-induced rise in liver IGF-I mRNA (-27%) and peptide (-32%) and of the serum IGF-I level (-26%), and concomitantly inhibited GH- but not IGF-I-stimulated body weight gain (-31%), tibial epiphyseal width (-14%) and bone growth rate (-24%). Furthermore, octreotide significantly reduced the GH-induced increase of the number of IGF-I immunoreactive chondrocytes in all layers (except in the upper hypertrophic zone) of the tibial growth plate cartilage ($P < 0.0001$ for stem cell and proliferative zone and < 0.0005 for lower hypertrophic zone). These findings demonstrate that octreotide does not interfere with IGF-I action but rather with local GH-stimulated IGF-I production in the growth plate. Thus, besides inhibiting pituitary GH secretion, octreotide exerts inhibitory peripheral effects on GH-stimulated longitudinal bone growth. Although our results cannot completely exclude that circulating endogenous IGF-I contributes to skeletal growth, they are rather compatible with the concept that skeletal growth is essentially determined by local IGF-I-mediated GH action at the level of the growth plate.

2.2 Divison of Orthopaedic Biomechanics

The activities of this Division are directed towards two major areas of research: basic and clinical orthopaedic biomechanics (BCB) and computer assisted surgery (CAS).

In basic and clinical biomechanics, the major areas of research are state-of-the-art implant evaluations, muskuloskeletal injury mechanisms and appropriate treatment strategies. Research methodologies involve primarily *in vitro* and *ex vivo* experiments, as well as mathematical (finite element) models. The focus of the work is the biomechanics of the normal and pathologic human spine. Other anatomic areas of interest are the hip and shoulder.

Research in the area of computer assisted surgery covers orthopaedic-, ENT-, maxillo-facial-, and dental surgical procedures. Proposed and established CAS-systems allow advanced image data acquisition and processing, pre-operative surgical planning and simulation, and intra-operative real-time control and visualization of surgical tools.

The Orthopaedic Biomechanics Division can be reached through the World Wide Web (WWW) at http://cranium.unibe.ch or at www.mem.unibe.ch.

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2.2.1 Computer Assisted Surgery (CAS)

Estimating Registration Accuracy Using a Probability-based Approach
Bächler R., Nemec B., Bunke H. and Nolte L.-P.

Objectives: To develop and evaluate a method for reliable registration accuracy estimation using a probability-based approach. In addition, the resulting estimate shall be visually presented to the user.
Background: In computer-assisted surgery based on three-dimensional image data (e.g, CT or MRI), registering the patient's anatomy with the image data is the most important step intraoperatively. However, appropriate means to estimate the registration accuracy and present this to the surgeon are lacking in current systems. Most efforts to present some sort of feedback are based on the mathematical model used for registration but do not really account for the anatomy being registered.
Design/Methods: A probability-based method has been implemented that can be applied to both paired-points and surface-based registration algorithms. Using the geometric configuration of the planned landmarks and intraoperatively captured points, it is possible to calculate *s*-percentiles of a worst-case error transformation. These *s*-percentiles represent the maximum error *e* for any given point in the volume with a certainty of *s* percent. For surface-based registration, the geometry of the anatomy being registered is used to calculate the *s*-percentiles. In order to provide the surgeon with a visual feedback, it is now possible to calculate a volume consisting of all points with a maximum error *e*

given a certainty *s* and display the resulting "confidence volume" by intersecting it with a 3D representation of the anatomy being registered.
To evaluate the accuracy of the developed error model, points were defined in the CT model and subsequently used for paired-points and surface-based registration. Applying random errors to the point data in order to simulate digitizing errors and random translations for the registration algorithms to start with, it is possible to calculate the actual deviation of any given point from its true location and thus compare the correlation of the confidence volumes with the actual error distribution.
Results: Initial tests using a CT model of a plastic vertebra and appropriate paired-points and surface points have shown a high correlation of the confidence volumes with the actual error distribution. Ongoing tests with multiple models are evaluating the accuracy of the presented method for other anatomical regions, e.g., the hip area.
Conclusions: Confidence volumes allow to represent the expected accuracy of paired-points and surface-based registration with respect to the anatomy being registered. The result can be easily interpreted by visual inspection, and adjusting the confidence *s* and the maximum allowable error *e* the computation of the confidence volumes can be fine-tuned to the requirements for the planned intervention.
Funded within NCCR CO-ME (http://www.co-me.ch/)

Image Guided Therapy in Otorhinolaryngology, Maxillo-Facial and Reconstructive, and Dental Surgery
Bächler R., Wyser U., Wong S. and Caversaccio M.

Objectives: Surgical interventions in the head area are extremely common in our society and a large number of these interventions can be carried out safely. However, there is considerable risk of inadvertent penetration of the cranial vault in sinus and skull base surgery, especially among patients in whom the normal anatomy has been altered through prior surgery, malformation, post-trauma, or through disease progression, e.g., tumors at the skull base. Complex reconstructive maxillo-facial as well as dental implant surgery suffer from insufficient means for planning and accurately executing the intervention, as only two-dimensional image date can be presented to the surgeon and no intraoperative navigation device exists. On the other hand, image guided therapy in otorhinolaryngology (ORL) has been performed for more than 10 years, demonstrating its potential to enhance the safety and accuracy of surgical interventions, especially in revision and tumor surgery.
This project is aimed at developing enabling tools for planning, intraoperative navigation, training, and education in the area of ORL, maxillo-facial, and dental surgery. One focus is to develop a planning module for maxillo-facial reconstructive surgery that allows accurate planning of osteotomies, and distraction and reorientation of multiple bone fragments. This provides the basis for the intraoperative navigation system that shall allow an easy to use and straightforward realization of the preoperative plan. This requires the integration

of current surgical instruments into the system, as well as the development of specific tools to help during the often tedious reorientation phase. A particular aspect is to evaluate the use of dexterity enhancement capabilities for this task. As many forms of pre- and intraoperative image modalities are present for interventions in the head area, the image-based guidance information must be presented to the surgeon in an ergonomic way. One possibility that will be explored is image injection into the surgical microscope's view-path.
Funded within NCCR CO-ME (http://www.co-me.ch/)

A Fast Impingement Detection Algorithm for Computer Aided Orthopaedic Surgery
Hu Q., Langlotz U., Lawrence J., Langlotz F. and Nolte L.-P.

For simulation in computer aided surgical interventions the detection of impingement between parts of the patient's anatomy and/or implants is often of key importance. Impingement (collision) detection methods used in the existing literature seem to be unsuitable for two reasons. First, a polyhedral approximation of an anatomical model is not appropriate, since medical images are quite irregular and are essentially non-linear. Secondly, geometric and temporal coherences are not always available, since just final results may be of interest. This paper describes the development of a fast and accurate impingement detection algorithm for medical applications. The presented algorithm takes implicit object models from reconstruction of anatomical CT data which represent complicated anatomical structures. To speed up the detection procedure, a lookup table and a linear transform are used so that searching for impingement between any two objects becomes a problem of calculating spatial indices and checking the lookup table. For any given transformation, the algorithm could perform impingement detection of two objects within 0.1 second on a 167MHz Sun UltraSPARC1 workstation. Experimental results concerning accuracy, reliability, and speed are given for a phantom and a patient's data set. This algorithm provides a general-purpose impingement detection method in the sense that objects can be of any shape, and it can be extended to any number of objects in the scene.

Comparison of Three Different Ultrasound B-Mode Calibration
Kowal J., Amstutz C. and Nolte L.-P.

Objectives: Precise transducer calibration is an essentially prerequisite for a reliable surface registration based on ultrasound B-Mode imaging facilities. The focus in this study is on comparing two existing B-Mode transducer calibration methods with a new calibration method, and performing calibration experiments and accuracy tests involving each of the implemented calibration procedures with respect to clinical usability and attainable calibration precision.
Design/Methods: In addition to the proposed calibration method, two established procedures the Three Wire Method proposed by Carr J. [1] in 1996

and Cambridge Calibration Method proposed by R.W. Prager et al. [2] in 1998 have been implemented and analyzed. They were used as reference methods in extensive accuracy tests enabling the comparison of calibration accuracy as well as the time and space requirements for the different methods. A trained observer performed twenty calibration trials for each method.
Results: All calibration attempts were completed successfully except for two Three Wire Calibrations. The time measurements performed during the calibration experiments and the space consumption indicate a distinct benefit in favor of the proposed calibration method. The results of the subsequent accuracy tests are all in the same order of magnitude with respect to the clinical application accuracy. No statistically relevant differences have been found.
Conclusions: The suggested calibration method offers decreased time and space consumption while retaining a calibration precision equivalent to the reference methods.

A Novel Concept Introducting Soft Tissue Consideration into an Intra-operative Planning and Navigation System for Total Knee Arthroplasty
Kunz M., Langlotz F., Strauss J.M., Rüther W. and Nolte L.-P.

Successful total knee arthroplasty requires component alignment according to the mechanical axes and restoration of ideal knee kinematics. This requires adequate ligament balancing, stable tibia-femoral and patello-femoral joints, and a non-restricted range of motion. We developed a computer assisted total knee arthroplasty system to help the surgeon achieving more intraoperative accuracy. An OPTOTRAK camera is used to track relative motions between femur, tibia, and instruments. In contrast to other systems we avoid fixation of reference bases onto acetabulum and foot. The surgeon generates a representation of the patient's anatomy using the technique of "surgeon defined anatomy". Based on recorded landmarks the system calculates the femoral and tibial mechanical axes, the position of the knee joint line, the level of the defects on femoral and tibial side, the anatomically best fitting femoral component size, the femoral ventral level, and the natural tibial rotation. These values enable an initial planning situation, which features alignment of the tibial and femoral distal resection planes according to the mechanical axes as well as the definition of the anterior and posterior femoral resection planes with respect to the ventral cortex and the prosthesis design. To consider soft-tissue behaviour the surgeon loads both collateral ligaments in extension and flexion, and the system records the relative positions of femur and tibia. A simulated postoperative situation is displayed permitting soft-tissue balancing and modification of the initial plan. Finally the system graphically guides the surgeon to perform the planed resections. During a clinical study we performed thirteen total knee arthroplasties. Postoperatively passive extension was 0.8-4.2° (mean 1.9°) in the coronal plane and 0.2-3.9 (mean 1.8°) in the sagittal plane. Varus-valgus instability was 7.2°.

Development and Verification of an Non-CT Based Total Knee Arthroplasty System for the LCS

Kunz M., Langlotz F., Strauss J.M., Rüther W. and Nolte L.-P.

Background: The postoperative result of a total knee arthroplasty strongly depends on surgical performance. Since the classical instrumentation does not allow the surgeon to find the optimal positions of components in any situation and to perform an adequate ligament balancing, we developed a computer-assisted system of LCS-arthroplasty.

Design/Methods: An optoelectronic space digitizer is placed in the operating theater to track relative motions between femur, tibia, and instruments. By means of dynamic reference-based attached to these objects. The procedure starts with the registration of the mechanical leg axes. Therefore we developed a pivoting algorithm, which tracks possible acetabulum movements using a pointer placed on the spina iliaca instead of an invasively attached reference base. For the registration of the femoral, and tibial knee centers and the ankle center directly digitized landmarks are used. In a special procedure the surgeon records the ligament behavior. Based on these values the system guides the surgeon to perform an adequate soft-tissue balancing. The resulting ligament behavior and the landmarks are the basis for the planning step. Besides the possibility to manually adjust each parameter the planning step offers an automatic plan, which is determined with respect to the experiences of the classical implementation technique and the prosthesis design. Parameters, which are respected include: Saving of the joint line, and creating of uniform and balanced gaps. Finally the planned resection planes are precisely executed using LED-equipped cutting-jigs.

Results/Conclusions: The collected experiences in various in-vitro tests, where the postoperative Varus/Valgus angle was not larger than 1.5° shows that the system generates accuracy alignment of resection-planes. The results of the first clinical study will be available at the time of the conference.

Freehand Navigation for Arthroscopy Assisted Retrograde Drilling
Marx A., Kunz M., Sobau C., Beutler T., Ellermann A. and Nolte L.-P.

Objective: To develop and evaluate a novel computer aided technology for arthroscopy assisted retrograde drilling.
Background: Pro- and retrograde drilling is an accepted treatment for fibro-cartilaginous repair in orthopaedic surgery [1,2]. Perforating the sclerotic bone stock underneath e.g. an osteochondrosis dissecans can stimulate blood supply. The main technical challenge of this arthroscopy assisted procedure is to preserve the articular cartilage, while dealing with a complex three-dimensional morphology. Currently 2D fluoroscopy is used during the drilling process for an image interactive feedback. However, main drawbacks are radiation exposure and a limited accuracy due to the two-dimensional nature of the underlying fluoroscopic images. The goal of this work was to simplify this surgical procedure and make it accurate and reproducible through the use of computer assistance.
Design/Methods: Throughout this study the arthroscopic SurgiGATE® KneeACL navigation system (Medivision, Oberdorf, Switzerland) was used. Light modifications, such as a real-time depth indicator, were necessary to provide the surgeon with an appropriate feedback during the drilling procedure. No pre- or intraoperative imaging was necessary. Intraoperatively the surgeon defines the intraarticular target point with the arthroscopic navigated still hook and the entry point is recorded with the navigated drill. The drilling procedure is performed along the computer trajectory until the distance between entry and target minus the estimated cartilage thickness is achieved. The system was tested on four artificial bones (Synbone, Malans, Switzerland) and one fresh bovine femur. Three drills with different diameters (A=2.0mm, B=2.5mm and C=3.0mm) were used. A total of 350 drilling procedures (210 into artificial bones, 140 into bovine bone) were performed. After the procedure the following parameters were analysed:
a) drill depth, b) deviation of executed to planned trajectory and c) influence of drill bit diameter.
Results: Drill depths varied between 17.5 and 54.6 cm. Mean difference between planned and achieved drill trajectories was smaller than one millimeter (A=0.56mm, B=0.38mm and C=0.66mm).
Conclusions: The proposed image free navigation system allows to effectively perform retrograde drilling. Based on the results of our experimental study it holds potential to improve the accuracy and safety of this kind of approach, while simplifying the surgical procedure and avoiding excessive radiation exposure

Improvement of the Surgeon's Skills Using the SurgiGATE Hip Navigation System through a Virtual Supervisor for Total Hip Replacement
de Siebenthal J. and Langlotz F.

Feedback given by current users of the SurgiGATE navigation system for total hip replacement indicated that a supervising software module could have the

potential to steepen the initial learning curve. In particular during the planning procedure, the user's actions involve difficult tasks such as segmentation, landmark definition, and optimization of the placement parameters (position, orientation, and size of the cup). Consequently, the overall context during this step is demanding to the user and can induce a non-optimal use of the system. The aim of this work is to provide a supervising module which helps the surgeon to correct his/her interactions with the SurgiGATE system and to improve his/her skills to work with it. A supervising module is currently being implemented, and related studies of its impact on surgeons will be delivered. In a next step a supervising module will be implemented for the intraoperative tasks using the SurgiGATE system.

Design of a Web-Based Medical Database for Computer-Assisted Orthopaedic Surgery
Wu T., Müller G., Schkommodau E., Radermacher K., Langlotz F. and Rau G.

The recent development of computer-assisted orthopaedic surgery (CAOS) provides a great potential to improve clinical outcome. One key feature of CAOS is the introduction of computer-based technical systems to perform surgical missions incorporating advanced medical imaging modalities such as CT and MRI for data acquisition, preoperative planning, surgical simulation and optimization, intraoperative navigation, and robotic systems. As the number of CAOS applications increases, it becomes more and more essential to collect the related experience for both educational and developmental purposes. Within the framework of the European VŒU-project (Virtual European Orthopaedic University), a web-based medical database called "Virtual Observatory" will be developed to meet this demand by collecting data from cases of CAOS for several orthopaedic applications.

Computer Aided Less Invasive Stabilization (L.I.S.S) for Metaphyseal Fractures of Femur and Tibia
Zheng G., Grützner P. and Nolte L.-P.

Objectives: To design and evaluate a novel image guided navigation system to alleviate technique demand of recently introduced Less Invasive Stabilization (L.I.S.S) technique.
Background: Several studies have shown a direct relationship between complications of fracture treatment and invasive operative techniques which damage the blood supply to the bone, delay fracture healing, and increase the risk of infection. In recent years, a new type of bridging osteosynthesis has evolved using a so called L.I.S.S plate which is inserted between the muscles and the periosteum. However, the success of plating is technique dependent. Recently, fluoroscopy based navigation systems have been provided by various research groups. These novel navigation systems for the first time provide the missing link between intraoperative imaging information of the surgical morphology with the

surgical action in different surgical applications. In a variety of pro- and retrospective clinical trials these systems have proven to improve surgical safety and accuracy during reposition manoeuvres, insertion of implants, and improve surgical devices while significantly reducing the radiation exposure.
Design/Methods: Fractured bone fragment, surgical drill and screw drivers, the so called L.I.S.S osteosynthesis plates were instrumented with optoelectronic tracking markers. A three-dimensional virtual world is built based on the calibration procedure of computer aided fluoroscopy system (Hofstetter et al). Paired-Point matching is used to register CAD models of L.I.S.S osteosynthesis plates to the associated real world instrument. These calibrated surgical instruments are tracked by a navigator during their action on the bony anatomy and can be visualized interactively in the said virtual world. Starting from the contours determined on two or more registered fluoroscopic images, a virtual three-dimensional model is reconstrcted for each principal bone fragment and its projection is used to define an image area for the associated bone fragment. Real-time X-ray image reposition for each fragment is achieved which allows visual control of close reduction of fracture in the virtual space. The plate are positioned and fixed by means of minimally invasive technique through the virtual reality guidance of the navigation system. The same result can only be achieved in conventional surgical techniques by using a C-arm unit in constant mode, which implies a high radiation exposure for the patient and the surgical staff.
Results: In the foam coated model tests, a complete x-ray free long bone fracture reduction and L.I.S.S plate fixation was possible after taking a few single x-ray shots. We saw the system to be very accurate during the model testing. Our early clinical esperience (three patients) confirms the observation.
Conclusion: A novel image guided system has been developed which can provide a realistic intraoperative visual feedback of fracture reduction and implant positioning. This alleviates the technique demand for using L.I.S.S technique for treatment of metaphyseal fractures for femur and tibia.

Augmented Reality for Computer Aided Fluoroscopy Based Diaphyseal Fracture Reduction and Fixation
Zheng G., Kowal J., Grützner P. and Nolte L.-P.

Objectives: To develop an augmented reality system for computer aided fluoroscopy based diaphyseal fracture reduction and fixation.
Background: Although the introduction of computer aid fluoroscopy based navigation system has provided many advantages over the common fluoroscopy image based guidance, it still has such disadvantages as two dimensional projection representations of fragments and tools, difficulty to achieve alignment of fragments and no guidance for shaft plating techniques.
Design/Methods: Fractured bone fragment, surgical drill and screw drivers, various osteosynthesis plates were instrumented with optoelectronic tracking markers. A three-dimensional virtual world is built based on the calibration procedure of computer aided fluoroscopy system (Hofstetter et al). The projection model determined from the calibration procedure allowed display of

detailed three-dimensional geometric models of surgical tools and implants overlaid onto the X-ray images. Starting from the contours determined on multiple calibrated fluoroscopy images, a virtual three-dimensional model for each bone fragment is reconstructed. The projection of this model is used to determine the fragment projection image. Real-time tracking of the three-dimensional virtual fragment models in above virtual world and reposition of two-dimensional fragment projection images on each X-ray images make it easy to achieve reduction with an augmented reality. The virtual realistic represenation of surgical tools and osteosynthesis plates and nails provides a quality control for the whole fixation procedure.
Results: The proposed prototype solution gives the surgeon a realistic and interactive feedback of normally hidden surgical actions. First attempts with broken plastic bones look very promising. Early clinical experience (3 patients) is confirming the observation.
Conclusion: The existing work shows that a minimal invasive fracture reduction and fixation process could be improved using such a system.

A Hybrid CT-Free Navigation System for Total Hip
Zheng G., Marx A., Langlotz U., Widmer K.H., Nolte M., Bernsmann K., Buttaro M. and Nolte L.-P.

Objectives: To design and evaluate a novel CT-free image guided surgical navigation system for complete total hip arthroplasty (THA) based on our previously introduced computer aided system for acetabular cup placement.
Background: Several studies have shown a direct relationship between component malalignment and the risk of dislocation after THA. CT-based free hand navigation systems can assist the surgeon in properly placing the acetabular component and early encouraging clinical results have been reported. Robot-assisted systems have been reported to increase the percentage of surface contact between the implant and the bone but only femoral stem planning and execution are supported. A more recently introduced hybrid CT-free navigation system provides a reliable solution for acetabular cup placement by combining widely available image intensifier technology with modern free hand surgical navigation. To the authors' best knowledge no investigation has been reported in the literature on the use of CT-free navigation technology for complete THA.
Design/Methods: Our work is based on the SurgiGATE® module "CT-free Cup" (MediVision, Oberdorf, Switzerland). First, two patient specific reference coordinate systems (RCOS) are defined: (a) for the pelvis based on the so-called anterior pelvic plane (APP) concept and (b) for the femur using the posterior condylar axis and the medullary canal axis of proximal femur. A previously introduced hybrid concept is used for the associated landmark acquisition, which involves percutaneous point-based digitization and bi-planar landmark reconstruction using multiple registered fluoroscopy images. Various landmark based clinical variables are computed in real time: cup inclination and anteversion, antetorsion and varus/valgus of the stem, lateralization, and limp length discrepancy for complete THA. In addition, instrument actions such as

reaming, impaction, and rasping are visualized to the surgeon by superimposing virtual instrument representations onto the fluoroscopic images. A detailed validation of the system was done with an in vitro study using six Thiel-fixated full body cadaveric specimens. Accuracy of the system is verified by comparing the reported technique with the CT based approach. The system is being evaluated in an early clinical trial on 25 patients.

Results: Although the Thiel-fixated cadaveric specimens do only provide a limited bone contrast in the fluoroscopic images, promising results are obtained from our in vitro study. In particular, following average differences are found: (a) 3o for antetorsion, (b) 1o for varus/valgus, (c) 1.5 mm for lateralization, and (d) 3 mm for limb length discrepancy. During our early clinical trial, all newly developed software and hardware components do seem to effectively support the surgeon in placing both acetabular and femoral components.

Conclusions: A novel CT-free image guided surgical navigation system for THA has been developed. It allows the surgeon to control important clinical parameters, such as cup inclination and anteversion, antetorsion and varus/valgus of the stem, lateralization, and limp length discrepancy for complete THA. Statistical data from our early clinical trial will be available at the time of the CAOS-Symposium.

2.2.2 Basic and Clinical Biomechanics (BCB)

Flow-Induced Convective Transport of Solutes within the Intervertebral Disc

Ferguson S.J., Beutler T.E. and Nolte L.-P.

The intervertebral disc is the largest avascular structure in the body. Previous experimental and analytical studies have demonstrated that for small molecules diffusive transport alone fulfils the nutritional needs of disc cells. It has been often suggested that fluid flow into and within the disc may enhance the transport of larger molecules. The goal of the study was to predict the influence of load-induced interstitial fluid flow on mass transport in the intervertebral disc. An iterative computer modelling procedure was used to predict the convective transport of physiologically relevant molecules within the disc. To provide experimental data for computer model validation, the long-time creep and recovery response of bovine intervertebral discs was determined. An axisymmetric, poroelastic finite-element structural model of the disc was developed. The diurnal loading was discretised into fixed time steps. At each time step, the fluid flow within the disc due to compression or swelling was calculated. A coupled diffusion / convection model was then employed to calculate the effect of these fluid velocities on solute transport, with a constant concentration of solute being provided at the vascularised endplates and outer annulus. Loading was simulated for several diurnal cycles, and the relative convective and diffusive transport was compared for solutes with molecular weights ranging from 400 Da to 40 kDa by inclusion of appropriate diffusivity constants. Consistent with previous studies, fluid flow did not enhance the transport of low-weight solutes. During swelling, interstitial fluid flow increased the unidirectional penetration of large solutes by approximately 100%. Due to the

biphasic nature of disc loading, however, the net effect of convective transport over a full diurnal cycle was more limited (30% increase). The net fluid exchange over one entire diurnal loading cycle has only a modest influence on the transport of large molecular-weight solutes. However, convective transport during swelling is substantial. Further study is required to determine the significance of large solutes and the timing of their delivery for disc physiology.

Anterior Fixation in the Osteoporotic Spine: Cut-Out and Pull-Out Characteristics of Implants.
Ferguson S.J., Winkler F., Beutler T.E. and Nolte L.-P.

A new concept for the anchorage of anterior fixation implants in the osteoporotic thoracic and lumbar spine is presented. The SpiralBlade, currently used for proximal locking of femoral intramedullary nails, has been proposed as a suitable device for use in the osteoporotic spine, due to its broad, flat surface, which should provide resistance against cut-out of the implant through the vertebral body under dynamic loading. The cut-out and pull-out characteristics of this implant were tested. The SpiralBlade was tested with and without a supplementary insertion guide screw. Two commercial implants were tested for comparison: the VentroFix and the MACS-TL HMA (hollow monoaxial) screw. All implants were tested in osteoporotic human cadaveric vertebrae, using a modified in vitro testing protocol which simulated a full corpectomy model. Dynamic cyclic axial loading of 100N, 200N and 400N was applied for 1000 cycles at each load level. Following cyclic testing, the pull-out strength of the implant was measured. No significant differences were found in the cut-out performance between the SpiralBlade with guide screw and the VentroFix. Both implants maintained the angular alignment of the vertebral body in the frontal plane. The SpiralBlade inserted without a guide screw was prone to cutting-out and a substantial loss of angular alignment of the vertebral body. Cut-out of the HMA screw was significantly greater than with the other implants; an average angulation of 12° in the frontal plane was observed after testing. Two HMA screws fractured during testing. The VentroFix, with an average maximum pullout force of 1166 N, has a significantly higher resistance to pullout than the SpiralBlade with guide screw (417 N), the SpiralBlade (332 N) and the Aesculap HMA screw (298 N). The SpiralBlade may be an alternative to anterior screw fixation in the osteoporotic spine, offering the same cut-out resistance with one implant rather than two screws.

The Effect of Vertebroplasty on the Load Transfer in a Functional Spinal Unit
Polikeit P., Nolte L.-P. and Ferguson S.J.

Vertebroplasty, the percutaneous injection of bone cement into vertebrae, has been a promising advancement for the treatment of painful, osteoporotic compression fractures. Early clinical results indicate immediate, reliable pain

relief and a low complication rate. Experimental biomechanical studies have shown significant increases in stiffness and strength of the treated vertebral bodies. However, little is known about the consequences of cement augmentation for the adjacent, non-treated level. A rigid cement augmentation may be the explanation for the observed compression fractures in adjacent vertebral levels. To test this hypothesis experimental and finite element investigations were undertaken. The purpose of this finite element study was to determine changes in load transfer, stress and strain due to the augmentation with cement. 3D finite element models of a L2-L3 functional spinal unit (FSU) were developed. The geometry was based on reconstructed CT scans from a young, healthy cadaver specimen. The material properties of the bony structures, the ligaments and the disc were obtained from the literature of previous finite element studies. To simulate the vertebroplasty, the material properties of the cancellous bone of one vertebral body were changed to those of polymethylmethacrylate (PMMA) bone cement. Uniform compression load was applied to all models. The results of the treated FSU were compared to those of non-treated FSUs. The resulting trends were similar, irrespective of the cemented level. The cement augmentation of one vertebra increased the pressure in the nucleus pulposus. The overall displacement behaviour of the FSU was subsequently changed. The stresses and strains in the cancellous cores, the cortical shells and especially the endplates of the adjacent vertebra were increased. The treatment clearly altered the load transfer within the FSU. Percutaneous vertebroplasty offers an efficient tool for augmenting vertebral bodies. However, the increased stiffness and strength of the augmented vertebra is related with the decreased failure load, shown in our experimental studies, with the increased stresses and strains in the untreated vertebra and with an altered load transfer through the whole functional spinal unit as demonstrated by this finite element study. These results support the hypothesis that the presence of rigid cement augmentation may facilitate the subsequent collapse of adjacent vertebrae. Further study is required to determine the optimal reinforcement material and filling volume to minimise this effect.

The Influence of the Endplate for Intervertebral Cages in the Lumbar Spine: Finite Element Analysis

Polikeit A., Nolte L.-P. and Orr T.E.

Intervertebral cages have been a promising advancement to relieve low back pain. Clinical follow-up studies have mostly presented successful fusions. However, mechanical failure, subsidence and migration of the cage have also been reported. Presently, different designs of cages require different endplate preparations. The endplate support provides mechanical strength whereas its removal promotes graft incorporation. The shape and the strength of the endplate have been shown to vary across its surface. However, its influence during load transfer has not been investigated, as has been done for cancellous bone. The aim of this study was to evaluate the influence of the endplate quality on stresses within the vertebrae and to determine possible failure mechanisms, using finite element (FE) analysis. A simplified model of a lumbar functional spinal unit was used to perform parametric analysis. Endplate materials were varied to represent a wide spectrum of bone qualities, ranging from the stiffness of the underlying

cancellous bone up to half that of cortical bone (e.g. 100, 600, 1000, 6000 MPa). One model with a cage and one without were developed. Contact elements with friction were used at the interface between the cage and the endplates. A uniform compression load of 1000 N was applied. With increasing endplate stiffness, the cortical shell stresses were found to be slightly reduced for the intact case, and to be increased after cage insertion. The results demonstrated that the greater the endplate modulus, the higher the stresses were in the endplate. The opposite was found for the cancellous bone, e.g. a stronger endplate reduced the stresses in the cancellous bone. In all cases, increasing the endplate modulus led to more prominent changes in the stress values after cage insertion as compared to the intact case.

Creation of a Finite Element Model for the Calculation of the Loading of Individual Dental Implants in the Mandible
Stern A., Ferguson S.J., Bächler R. and Nolte L.-P.

Current surgical planning and navigation software provides the surgeon with an efficient and accurate tool with which the final placement and orientation of metallic implants can be planned in the pre-operative stage, and then precisely achieved during surgery. Predictions of the resulting mechanical environment, however, cannot be made. Current computer simulations of the mechanics of metallic implants use complex finite-element models to provide accurate predictions of the stresses acting within the implant and the surrounding bone following implantation. However, extensive time is required to build such models, to achieve a solution, and then to interpret and present the results of the analysis. It is our goal to fuse these two technologies to incorporate real-time stress analysis into future surgical planning and navigation software, so that the surgeon is provided with immediate feedback of the influence of implant placement and orientation on the final mechanical environment about the implant. To that end, a project was completed comparing the accuracy and solution time required for a complex, three-dimensional finite element model of a typical implant placement with a simplified model using a less extensive mathematical formulation. For this study, our focus was the placement of dental implants in the mandible, as the implant geometry is well defined, but the definition of the surrounding bone is challenging. Solutions obtained with models composed of simplified finite elements correlated well with those obtained with a full three-dimensional model, but at a fraction of the computational time. The results of this study provided a framework for integrating automated, real-time stress analysis into future surgical planning software.

3 PUBLICATIONS

3.1 Division of Biology

Original Articles

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Book Articles

Buckwalter J.A., Mow V.C. and Hunziker E.B.: Articular cartilage injury and repair in the development and progression of Osteoarthritis. In: Moskowitz RW, Howell DS, Altman RD, Buckwalter JA, Goldberg VM, eds. Osteoarthritis. Diagnosis and Medical/Surgical Management: Concepts of Cartilage Repair in Osteoarthritis, 101-114, 2001

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3.2 Division of Orthopaedic Biomechanics

Original Articles

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Cripton P.A., Sati M., Orr T.E., Bourquin Y., Dumas G.A. and Nolte L.-P.: Animation of in vitro biomechanical tests. Journal of Biomechanics. 34: 1091-6, 2001

Ferguson S.J., Bryant J.T. and Ito K.: The material properties of the bovine acetabular labrum", Journal of Orthopaedic Research, 19: 887-96, 2001

Frei H., Oxland T.R., Rathonyi G.C. and Nolte L.-P.: The effect of nucleotomy on lumbar spine mechanics in compression and shear loading. Spine. 26: 2080-9, 2001

Gautier E., Bächler R., Heini P.F. and Nolte L.-P.: Accuracy and safety of computer guided screw fixation of the sacroiliac joint – A laboratory study, Clin Orthop Rel Res, 393: 310-317, 2001

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Hüfner T., Pohlemann T., Tarte S., Gänsslen A., Citak M., Bazak N., Culemann U., Nolte L.-P. and Krettek C.: Computer-assisted fracture reduction: Novel method for analysis of accuracy. Comp Aid Surg, 6, 153-159, 2001

Nydegger T., Oxland T.R., Hoffer Z., Cottle W. and Nolte L.-P.: Does anterolateral cage insertion enhance immediate stabilization of the functional spinal unit? A biomechanical investigation. Spine. 15: 2491-7, 2001

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Slomczykowski M.A., Hofstetter R., Sati M., Krettek C. and Nolte L.-P.: A novel computer assisted fluoroscopy system for intraoperative guidance: Feasibility study for distal locking of undreamed femoral nails. J of Orthop Trauma, 15(2): 122-131, 2001

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Book Articles

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Wu T., Müller G., Schkommodau E., Radermacher K., Langlotz F. and Rau G.: Design of a web-based medical database for computer-assisted orthopaedic surgery, Lemke H.U., Inamura K., Doi K., Vannier M.W., Farman A.G. (eds.), Amsterdam, Lausanne, New York: Elsevier Science B.V., 331-337, 2001

4 RESEARCH PROJECT GRANTS

The M.E. Müller Institute for Biomechanics is indebted to the M.E. Müller- and AO-/ASIF-Foundations for their generous annual contributions to its budget.

The support of a large number of specific research projects by various foundations and firms, in particular the Swiss National Science Foundation, is gratefully acknowledged.

* * *

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Bernsmann K., Stäubli H.U. and Sati M.: Computerised in situ planning and guidance of ACL graft placement. Clinical application to a variety of surgical techniques, AO/ASIF-Foundation, Bern. 1.1.99-31.12.2001

Chiquet M.: Regulation of extracellular matrix protein expression by mechanical stress. Swiss National Science Foundation, Bern. 1.4.1999-31.3.2002

Ferguson S.J.: Marrow Contact channel occlusion and disc degeneration, Natural Sciences and Engineering Research Council, Canada. 1.5.2000-30.4.2002

Ferguson S.J.: Polymer implant fixation: thermal and mechanical characteristics at the bone/implant interface, WoodWelding, Switzerland. 1.6.2001-30.9.2001

Ferguson S.J.: Marrow contact channel occlusion and disc degeneration, Natural Sciences and Engineering Research Council, Canada. 1.5.2000-30.4.2002

Ferguson S.J. and Beutler T.E.: Tuberosity fixation in hemiarthroplasty of the proximal humerus in traumatic cases, DePuy, France. 1.9.2001-31.1.2002

Ferguson S.J. and Nolte L.-P.: Biomechanical investigation of a proposed anterior spinal anchorage implant. Phase II: Cut-out and pull-out characteristics, Stratec Medical. 1.1.2001-31.5.2001

Hunziker E.B.: Osteoarthritic disease modification by intra-articular injection of bone-marrow-derived mesenchymal stem cells. Osiris Therapeutics, Baltimore, MD, USA. 1.10.2000-30.6.2002
Hunziker E.B.: Osteoarthritis prevention and chondroprotection, Synovart, Toronto, Canada. 1.1.2001-30.6.2002

Hunziker E.B., Park Y.D. and Sugimoto M.: Synovial-derived chondrogenic precursor cells for articular cartilage repair, Swiss National Science Foundation, Bern. 1.10.2001-30.9.2004

Hunziker E.B., Quinn T.M. and Wong M.: Development, structure and function of normal and diseased articular cartilage, Swiss National Science Foundation, Bern. 1.7.1998-30.6.2001

Grodzinsky A. and Hunziker E.B.: Mechanisms of chondrocyte response to mechanical stimuli, NIH, Bethesda, MD, USA. 1.10.1998-30.09.2003

Grützner P. and Wentzenzen A.: An advanced trauma module based on fluoroscopic navigation technology, AO/ASIF-Foundation, Bern. 1.10.1999-30.9.2001

Langlotz F.: A Versatile Preoperative Planner for Orthopaedic Surgery (project within the National Center for Competence in Research "CO-ME – Computer Aided and Image Guided Medical Interventions"), Swiss National Science Foundation. 1.7.2001-30.6.2005

Langlotz F. and Nolte L.-P.: Entwicklung eines Simulators und eines intraoperativen Navigationssystems zur computerunterstützten Insertion von Hüftgelenksimplantaten, Stratec Medical, Oberdorf. 1.6.2000-30.11.2001

Nolte L.-P. and Langlotz F.: VŒU - A virtual orthopaedic European University, 5th Research Framework Program of the European Union. 1.5.2000-30.04.2003

Nolte L.-P.: A novel approach for the percutaneous location of bone structure by ultrasound; towards new minimally invasive computer assisted surgery, Swiss National Science Foundation, Switzerland. 1.10.99-1.10.2002

Nolte L.-P.: Dental navigation, Institut Straumann, Waldenburg, Switzerland. 1.1.2000-31.3.2002

Nolte L.-P. and Langlotz F.: VŒU - A virtual orthopaedic European University, 5th Research Framework Program of the European Union, 1.5.2000-30.04.2003

Orr T.E. and Bellare A.: Assessing deformation mechanisms and microdamage in cortical bone, Swiss National Science Foundation, Switzerland. 1.10.1999-1.10.2001

Studer D.: Vitrifying, cutting, observing – the dream method for electron microscopy. Swiss National Science Foundation, Bern. 1.10.2000-30.9.2003

Trueb B.: Structure and function of novel cartilage proteins. Swiss National Science Foundation, Bern. 1.10.00-30.9.03

Trueb B: Applications of the FGFRL1 gene and of the protein encoded thereby. Osiris Therapeutics, Baltimore MD, USA. 1.10.01-30.9.02

Unser U. and Thévenaz Ph.: Fluoroscopy-based 3D/2D registration for minimally-invasive approaches in trauma and spine surgery, AO Research Commission, Switzerland. 1.10.2000-30.9.2002

Wong M., Hunziker E.B. and Hubbell J.A.: Regulation of matrix synthesis in tissue-engineered constructs for cartilage repair, Swiss National Science Foundation. 1.4.2000-31.3.2003

5 TEACHING ACTIVITIES

University of Basel:

- 2549 and 4562: New literature in extracellular matrix biology

University of Bern:

- Cytologisch-Histologisches Praktikum für Medizin- und Tierarzt-Studenten im 1. Jahr

- S4001/W4001: PBL (Problem Based Learning)-Curriculum, Medical Faculty: Tutorial (1. year and 3. year)

- S4001: PBL (Problem Based Learning)-Curriculum, Medical Faculty: Concept Lecture KV 26-1; Introductory Lecture EV 28-3

- S7342: Applied Molecular Biology, interfakultäre Vorlesung für Vorgerückte

- W7322: Connective Tissue Research, Kolloquium

- W7260.0: Zellbiologie II, Vorlesung für Studierende der Biologie und Biochemie

- W7311.1: Praktikum zu Immunologie II, für Studierende der Zellbiologie, Mikrobiologie und Immunologie

- S7274.1: Praktikum zu Mikrobiologie II, für Studierende der Mikrobiologie und Biochemie

- W4001: Vorklinisch problemorientierter Unterricht (VPU) für Studierende der Human- und Zahnmedizin

Inselspital Bern:

- Biomechanics for Physiotherapists

6 FELLOWSHIPS, DISSERTATIONS AND MASTER THESES

6.1 Dissertations Completed

Hoigné D., Dr. med., University of Bern, Bern, 2001
Beiträge zur Realisierung der Schaftinsertion mittels computerassistierter Freihand-Navigation bei der totalen Hüftendoprothese: Definition der Achsen und des Antetorsionswinkels am Femur. Referenzierung und Registrierung des Femurs

Wiedemann M., Dr. phil. II, University of Bern, Bern, 2001
Characterization of two clones from a subtracted, cartilage-specific cDNA library: MGP and FGFRL1

6.2 Masters Theses Completed

Stern A., Diplom, Fachhochschule-Furtwangen, 2001
Erstellen eines Finite Elemente Modells zur Berechnung der Belastung einzelner Dentalimplantate im Unterkiefer [Creation of a finite element model for the calculation of the loading of individual dental implants in the mandible]

Nemec B., University of Bern, Bern, 2001
Validierung von Registrierungen in der Computerassistierten Chirurgie, Institut für Informatik und angewandte Mathematik

7 HONORS AND AWARDS

03.2000 to date Hunziker E.B.: Chairman of the Special Review Panel of the German Ministry of Education and Science for Tissue Engineering Projects, Germany

03.2000 to date Hunziker E.B.: Member of the National Institutes of Health-review panel for tissue engineering and related bioengineering research partnership grant applications (NIH, Bethesda) USA

01.2001 Wong M.: Iwao Yasuda Award for Outstanding Contribution to Biomedical Research, Society for Physical Regulation in Biology and Medicine

02.2001 Nolte L.-P.: Maurice E. Müller Award for Excellence in Computer Assisted Surgery, 1st Annual Meeting of the International Society for Computer Assisted Orthopaedic Surgery, Davos, Switzerland

02.2001 Wong M.: Program Committee, Orthopaedic Research Society

7.-10.02.2001 Nolte L.-P.: Chairman of the 1st Annual Meeting of the International Society for Computer Assisted Orthopaedic Surgery, Davos
07.2001 Nolte L.-P.: Co-Director of the National Center for Competence in Research: "Computer Aided and Image Guided Medical Interventions" CO-ME (http://www.co-me.ch)

5.-8.07.2001 Nolte L.-P.: Chairman of CAOS/USA 2001 Fifth Annual North American Program on Computer Assisted Orthopaedic Surgery, Pittsburg, PN, USA

09.2001 Ferguson S.J., Berlemann U., Polikeit A., Heini P.F. and Nolte L.-P.: Biomechanica award for the paper „Are adjacent vertebrae at risk following vertebroplasty?", Biomechanica IV, Davos, Switzerland

09.2001 Langlotz U., Grützner P.A., Bernsmann K., Wälti H., Rose E., Bächler R., Korber J., Tannast M. and Nolte L.-P.: HAP Paul Award, International Society for Technology in Arthroplasty (ISTA), Maui, Hawaii, USA: A Hybrid CT-free Navigation System for Acetabular Cup Placement

11.2001 Chiquet M.: Promotion to "Titularprofessor" Medical Faculty of the University of Bern

12.2001 Tannast M.: 1. Price of the Faculty of Medicine for the Dissertation: Die Berechnung von Anteversion und Inklination bezüglich der Beckenfrontalebene. Eine CT-basierte computer-unterstützte Studie von 37 Totalhüftendoprothesen

28.07.-2.08.2002 Hunziker E.B.: Chairman of the Gordon Research Conference of Musculoskeletal Biology and Bioengineering, Andover, NH, USA

2003 Hunziker E.B.: Co-founder and vice-chair of the Gordon Research Conference for Cartilage Biology and Pathology, Ventura, CA, USA

8 GUEST PRESENTATIONS

1.06.2001 - Dr. med. U. Wehrli: Ligament Balancing. Orthopaedic and Traumatology Department, Zieglerspital, Bern, Switzerland

8.06.2001 - Prof. M. Oka, M.D. Ph.D.: Development of Artificial Articular Joint or Role of Uppermost Superficial Layer of Articular Cartilage in Lubrication Mechanism of Joints. Director of the Institute for Frontier Medical Sciences, Kyoto University, Kyoto, Japan

18.09.2001 - PD Dr. med. K. Klaue: Preoperative Planning and Simulation of Perixocal Osteotomies. Orthopaedic Department, Hotspital San Giovanni, Bellinzona, Switzerland

21.09.2001 - Dr. Donal McNally: Dynamic Imaging of Internal Structure of Intact Intervertebral Discs. University of Nottingham, Faculty of Engineering, Nottingham, U.K.

7.11.2001 - J. Paige Smallhorn: Finite Element Modeling of Annular Lesions in the Lumbar Intervertebral Disc. Centre for Rehabilitation Science and Engineering, Queensland University of Technology, Brisbane, Australia

17.12.2001 - Prof. Rodrigo Pesantez: Biological Fracture Fixation Using Plates. Colegio Mayor de Nuestra Senora del Rosario and Fundacion, Santa Fe de Bogota, Colombia

9 PERSONNEL

9.1 Faculty

Hunziker Ernst B., M.D., Prof.	Director	11.89 -

* * *

Nolte Lutz-Peter, Ph.D., Prof.	Division Head	05.93 -
Trueb Beat, Ph.D., Prof.	Deputy Division Head	04.95 -
Chiquet Matthias, Ph.D., Prof.	Research Group Head (80%)	05.95 -
Bächler Richard, Ph.D.	Research Group Head	06.96 -
Ferguson Stephen, Ph.D.	Research Group Head	02.00 -
Langlotz Frank, Ph.D	Research Group Head	05.93 -
Studer Daniel, Ph.D.	Research Group Head (20%)	03.92 -
Wong Marcy, Ph.D., PD	Research Group Head (80%)	02.92 -

9.2 Research Associates

Amstutz Christoph, M.D.	Ph.D.-Student	01.99 -	12.01
Bärtschi Stefan, cand. Phil. Nat.	Diploma-Student	11.01 -	
Barbieri Carrera Roberto, dipl. Ing.	Assistant	08.00 -	06.01
Beutler Thomas, dipl. Ing. HTL	Assistant	05.99 -	
Buttaro Martin, M.D.	Guest Surgeon	09.00 -	10.01
Crottet Denis, dipl. Ing./Phys.	Ph.D.-Student	05.01 -	
de Siebenthal Julien, dipl. Phys.	Ph.D.-Student	07.00 -	
Douta Gisèle, dipl. Inf.	Ph.D.-Student	12.01 -	
Driesang Iris, Dr. med.vet.	Assistant	06.96 -	
Griessen Roland, dipl. Ing. HTL	Assistant	11.96 -	
Goodwin Kelly, M.S.	Assistant	06.00 -	
Huber François, Dr. Phil. Nat.	Postdoc	08.01 -	
Hunenbart Stefan, dipl. Ing.	Ph.D.-Student	09.99 -	05.01
Ioppolo James, dip. Ing.	Ph.D.-Student	08.01 -	
Jurgen Stina, dipl. Ing.	Ph.D.-Student	05.01 -	
König Benjamin, M.D.	Assistant	01.01 -	03.01
Kouadri Mostéfaoui S., dipl. Inf.	Ph.D. Student	07.00 -	03.01
Kowal Jens, dipl. Ing.	Ph.D.-Student	10.97 -	
Kubiak Monika, dipl. Inf.	Ph.D.-Student	11.99 -	
Kübele Petra, dipl. Biol.	Assistant	11.01 -	
Künzi Manuel, dipl. Ing.	Assistant	12.01 -	
Kunz Manuela, dipl. Inf.	Ph.D.-Student	06.98 -	
Li Bo, dipl. Phil. II	Ph.D.-Student	06.99 -	
Liang Jane, Mech. Ing.	Ph.D.-Student	08.01 -	
Liu Jubei, Dr. Ing.	Postdoc	11.01 -	

Marx Axel, M.D.	Exchange Student	04.01 -	
Montanari Javier H., Biom. Ing.	Ph.D.-Student	10.00 -	
Nemec Bernhard, Inf.	Student	03.00 -	07.01
Nolte Michael, Biomed. Ing.	Exchange Student	08.01 -	
Park Yong Doo, Dr. Biomed. Ing.	Postdoc	01.01 -	
Polikeit Anne, dipl. Ing.	Ph.D.-Student	03.98 -	
Robinson Leanne, Mech. Ing.	Exchange Student	06.01 -	
Rodriquez Paloma, Mech.Ing.	Exchange Student	07.01 -	
Sarasa Renedo Ana, lic. Biol.	Ph.D.-Student	09.01 -	
Schild Christof, dipl. Phil. II	Ph.D.-Student	06.99 -	
Schoch Reto, med. Ing.	Student	07.01 -	09.01
Schulze Ina, Biomed. Ing.	Exchange Student	08.01 -	
Siegrist Mark, dipl. Phil. Nat.	Assistant	07.97 -	
Sinnoqrot Hayel, B.Sc. Inf.	Exchange Student	08.01 -	
Stern Andreas, cand. Ing.	Guest Student	09.00 -	02.01
Sun Jiuai, Dr. Ing.	Postdoc	11.01 -	
Sugimoto Masayuki, M.D.	Postdoc	03.00 -	
Tarte Ségolène, dipl. Ing.	Ph.D.-Student	09.99 -	
Trächslin Jonas, Dr. Phil. II	Postdoc	02.01 -	04.01
Van Schrojenstein Esther, cand.Ing.	Exchange Student	09.00 -	02.01
Wang Gongli, dipl. Ing.	Ph.D.-Student	04.00 -	
Wälti Heinz, dipl. Inf.	Assistant	12.96 -	
Wiedemann Markus, dipl. Phil. II	Ph.D. Student	03.97 -	04.01
Winkler Florian	Medical Student	01.01 -	05.01
Wong Ka Ho Stanley, El. Ing.	Exchange Student	07.01 -	
Wyser Urban, Mech. Ing.	Ph.D.-Student	08.01 -	
Xue Jinghao, El. Ing.	Postdoc	11.01 -	
Zheng Guoyan, Dr. Ing.	Postdoc	03.99 -	

9.3 Technical and Administrative Staff

Berger Elke	Res. Technologist (50%)	01.90 -	
Fahnemann-Nolte Karin	Secretary (60%)	03.96 -	
Fiechter Esther	Secretary (90%)	07.95 -	
Gaschen Véronique	Chief Technician	09.95 -	
Gerber Thomas	Apprentice in Fine Mechanics	08.01 -	
Gnahoré Esther	Secretary (70%)	12.90 -	
Haller Manuela	Secretary (50%)	11.00 -	
Howald Lana	Res. Technologist (50%)	03.01 -	09.01
Hutzli Walter	Aid Lab. Technician	11.89 -	
Kapfinger Eva	Res. Technologist (75%)	11.89 -	
Mathys Isabelle	Res. Technologist	08.00 -	06.01
Mühlheim Erland	Mechanicien (60%)	01.92 -	
Neseli Güler	Res. Technologist	08.96 -	07.01
Neuenschwander Annelies	Secretary (35%)	04.95 -	

Nüssli Simon	Res. Technologist	12.00 -	
Reist David	Res. Technologist	07.97 -	
Rohrer Urs	Head Mech. Workshop	07.91 -	
Schenker Thomas	Chief Technician	04.95 -	02.01
Täschler Sara	Res. Technologist	08.00 -	
Trueb Judith	Res. Technologist	03.01 -	
Tunc-Civelek Vildan	Res. Technologist (80%)	09.99 -	

9.4 Scientific Consultant

Prof. Dr. Robert K. Schenk, Clinic for Oral Surgery, University of Bern, Switzerland

9.5 Guest Scientists

Dr. Thomas M. Quinn, Biomedical Engineering Laboratory, Department of Applied Physics, Swiss Federal Institute of Technology, Lausanne, Switzerland

Dr. Pierre Mainil-Varlet, Institute of Pathology, University of Bern, Bern, Switzerland

10 MISCELLANEOUS

10.1 Conferences Organized

1st Annual Meeting of the International Society for Computer Assisted Orthopaedic Surgery, Davos, Switzerland, February 7-10, 2001 (Nolte L.-P. Organizer)

4th International Meeting of the ICRS, International Cartilage Repair Society, Toronto, Canada, June 15-18, 2002 (Hunziker E.B. Co-Organizer)

CAOS/USA 2001 – Fifth Annual North American Program on Computer Assisted Orthopaedic Surgery, Pittsburgh, USA, July 6-8, 2001 (Nolte L.-P.: Co-Chairman)

1st Nordic Course on Computer Assisted Orthopaedic Surgery, Helsinki, Finland, August 30-September 1st, 2001 (Nolte L.-P.: Co-Chairman)

11th Swiss Cytomeet, Bern, October 24, 2001 (Chiquet M. Co-Organizer)

11 MEMBERS OF THE SCIENTIFIC ADVISORY BOARD (KURATORIUM)

Prof. Dr. R. Häusler, (President), Director HNO-Klinik, Inselspital, Bern
Prof. Dr. R. Friis, Dept. of Clinical Research, University of Bern, Bern
Prof. Dr. R. Ganz, Dept. of Orthopaedic Surgery, University of Bern, Inselspital, Bern
Mr. U.G. Jann, AO/ASIF-Foundation, Davos
Mr. A. Marti (Vice President), Erziehungsdirektion des Kantons Bern, Bern
Prof. Dr. H. Reuter, Dept. of Pharmacology, University of Bern, Bern
Prof. Dr. M.E. Müller, Honorary Board Member, President of the M.E.Müller Foundation, Bern