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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 Maurice E. Müller Institute for Biomechanics attained the legal status of a full University Institute on January .1, 1995, this decision having been reached by the Bernese Government on May 30, 1994 and approved by the State (Grosser Rat) on June 9, 1994. The objectives of the Institute are basic and applied biomechanical research of the locomotor system at the organism, tissue, cellular and molecular length scales. The Institute 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 Maurice E. Müller Institute for Biomechanics is currently under the Directorship of Prof. Ernst B. Hunziker, who was elected to this position by the Bernese Government in autumn of 1989.

Objectives

The Institute's efforts are directed towards the development of an integrated understanding of the structure and function of the musculo-skeletal system at the organism, tissue, cellular and molecular length scales, and the development and optimization of information, materials, and techniques for clinical application in the detection and treatment of musculo-skeletal diseases. It is thus conceived as a link between academic research, surgical practice and industrial development. Collaborations with various Research Institutes of the University of Bern, a number of other University Institutes, the Department for Orthopaedic Surgery at the Inselspital and other clinical partners, industrial enterprises as well as with the AO/ASIF Foundation's Research Institute in Davos, are therefore embraced in its functions.

Previous and Current General Research Program

Since the time of its foundation in 1981 until 1988, the MIB was directed by Prof. Stephan S. Perren. The goals of the Institute during this period were to study the normal and disturbed loading patterns of the locomotor apparatus, to improve our understanding of this system, and to promote the knowledge thereby gained in relation to the principles, techniques, instrumentation, and implants applied in orthopaedic surgery. In 1989, Prof. Ernst B. Hunziker took over the Directorship, and he has then extended the Institute's research activities to include basic and applied biological aspects of skeletal tissue structure and function at the tissue, cellular and molecular levels, such as biochemistry, molecular biology, microstructural preservation, histological-morphometric analysis, compatibility of implant materials, interfacial (adhesion) biology, mechanical properties, and metabolic cell- and tissue responses to mechanical stimuli. Research activities in the field of classical biomechanics are currently being continued by Prof. Lutz-P. Nolte, who broadened its scope and extended the Institute's research activities to include computer-assisted surgery. In 1993 Dr. Nolte was appointed Head of the Institute's Division of Orthopaedic Biomechanics. Prof. Hunziker is, in addition to

being Director of the Müller-Institute for Biomechanics, also the Head of the Institute's Division of Biology, of which PD Dr. Beat Trueb is Associate Head.

With these new dimensions, the Institute aims at an integrated approach to questions raised in connection with the biomechanics of the musculo-skeletal system, prostheses, endoprostheses, fracture treatment and novel biological treatment strategies.

Organization

The Institute is comprised of a staff of about 65 people, including 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, while those of the other involve basic and applied research in the biology of the musculo-skeletal apparatus. The two divisions collaborate with one another and are supported by a basic technical staff furnishing histological-, computer-, mechanical- and electronic services. The Institute of Biomechanics can be reached through the World Wide Web (WWW) at http://www-mem.unibe.ch.

Significance of Research Program

The research activities conducted at the MIB contribute to our basic understanding of the structure and function of the musculo-skeletal system and the control mechanisms operating at both the organ, tissue, cellular and molecular levels. The knowledge thereby gained will help us to further develop and optimize materials for clinical application, conceive novel biologically based treatment strategies and assist in a rational, scientific approach to the treatment of diseases of the musculo-skeletal system.

* * *

2 RESEARCH ACTIVITIES

2.1. Division of Biology

2.1.1 Molecular Biomechanics

The main activities encompassed within the scope of 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 connective tissues being the main tissues investigated. Current topics dealt with include the analysis of structural and functional properties of components contained in adult human articular cartilage, foetal cartilages and soft connective tissues. Newly-identified extracellular constituents are being cloned, sequenced and analyzed from a functional viewpoint.

* * *

Comparative Cytogenetic Mapping of the Gene for Human and Mouse Collagen XIV
Imhof M. and Trueb B.

Collagen XIV is a minor protein of the extracellular matrix associated with interstitial collagen fibrils. Since collagen XIV from mice has not yet been described, we have selected and characterized several clones for this protein from the mouse EST databank. Using one of the clones as a probe we have mapped the corresponding gene in the mouse genome and compared its localization with that of the human collagen XIV gene. The mouse gene (Col14a1) could be assigned to chromosome 15 band D by the FISH technique. The human gene (COL14A1) was assigned to chromosome 8 bands q23-q24.1. This assignment is in agreement with the localization of the undulin gene (UND), whose product has been suggested to be a variant of collagen XIV. Our results demonstrate that collagen XIV is another example of a gene that belongs to human/mouse homology group 90.

DRG Represents a Family of Two Closely Related GTP-binding Proteins
Li B. and Trueb B.

Recently we have identified a novel human GTP-binding protein that shares significant similarity with DRG, a developmentally regulated GTP-binding protein from the central nervous system of mouse. We could now demonstrate that both the human and the mouse genome possess two closely related drg genes, termed drg1 and drg2. The two genes share 62% sequence identity at the nucleotide and 58% sequence identity at the protein level. The corresponding proteins appear to constitute a separate family within the superfamily of the GTP-binding proteins. The DRG1 and the DRG2 mRNAs are widely expressed in human and mouse tissues and show a very similar distribution pattern. The human drg1 gene is located on chromosome 22 region q12, the human drg2 gene on chromosome 17 region p12. Distantly related species including C. elegans, S. pombe and S. cerevisiae also possess two drg genes. In contrast, the genomes of archaebacteria (Halobium, Methanococcus, Thermoplasma) harbor only one drg gene, while eubacteria do not seem to contain it at all. The high conservation of the polypeptide sequences between distantly related organisms indicates an important function of DRG1 and DRG2 in a fundamental pathway.

An α-Actinin Binding Site of Zyxin Is Essential for Subcellular Zyxin Localization and for α-Actinin Recruitment
Reinhard M., Zumbrunn J., Jaquemar D., Kuhn M., Walter U. and Trueb B.

The LIM domain protein zyxin is a component of adherens junctions, stress fibers and dynamic membrane areas and appears to be involved in microfilament organization. Chicken zyxin and its human counterpart display less than 60% sequence identity, raising concern about their functional identity. We have demonstrated now that human zyxin, like the avian protein, specifically interacts with α-actinin. Furthermore, we have mapped the interaction site to a motif of approximately 22 amino acids, present in the N-terminal domain of human zyxin. This motif is both necessary and sufficient for α-actinin binding, whereas a downstream region, which is related in sequence, appears to be dispensable. A synthetic peptide comprising human zyxin residues 21-42 specifically binds to α-actinin in solid phase binding assays. In contrast to full length zyxin, constructs lacking this motif do not interact with α-actinin in blot overlays and fail to recruit α-actinin in living cells. When zyxin lacking the α-actinin binding site is expressed as a fusion protein with green fluorescent protein, association of the recombinant protein with stress fibers is abolished and targeting to focal adhesions is grossly impaired. Our results suggest a crucial role for the α-actinin/zyxin interaction in the subcellular zyxin localization and in the microfilament organization.

Loss of Type VI Collagen in Experimental and in Most Spontaneous Human Fibrosarcomas
Trueb B. and Odermatt B.F.

Expression of type VI collagen, an adhesive protein of mesenchymal tissues, is significantly down-regulated after viral transformation of fibroblasts. Likewise, most cell lines derived from spontaneous mesenchymal tumors, including fibrosarcomas, rhabdomyosarcomas, leiomyosarcomas, chondrosarcomas, and liposarcomas, do not synthesize type VI collagen because they are not capable of expressing all the three polypeptide chains required for the assembly of a functional heterotrimeric molecule. When injected into nude mice, neither fibrosarcoma cells (HT1080) nor rhabdomyosarcoma cells (A204) initiate the synthesis of type VI collagen, suggesting that the inhibition is not caused by the deficiency of a paracrine factor. Immunohistochemical studies further illustrate that 15 out of 17 spontaneous adult fibrosarcomas are lacking type VI collagen in their tumor stroma. It is conceivable that the absence of this important adhesion protein contributes to tumorigenicity, invasiveness and/or metastasis of mesenchymal tumor cells.

2.1.2 Cellular Biomechanics

This research area concerns the mechanism by which fibroblasts in tissues exposed to large tensile stress, i.e. in 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. Fibroblasts are cultured on elastic substrates and subjected to controlled strain, in order to determine the effects on gene transcription of these

proteins. Such knowledge should help to devise means of manipulating not only the quantity but also the composition (and hence the mechanical properties) of repair tissue formed in response to injury.

* * *

Ectopic Induction of the Extracellular Matrix Proteins, Tenascin-C and Collagen XII by Stretch of Chicken Skeletal Muscle
Flück M., Tunc T. and Chiquet M.

Mechanical stimulation is essential for the homeostasis of connective tissues. A feedback mechanism must exist by which connective tissue cells sense mechanical stress acting on their extracellular matrix (ECM), and in turn remodel the ECM to adapt it to changing mechanical requirements. Extracellular matrix proteins tenascin-C and collagen XII are expressed in tissues bearing high mechanical stress such as periosteum, ligaments, and tendons. In normal skeletal muscle, tenascin-C locates exclusively to the myotendinous junctions linking muscle fibers to tendon, while collagen XII is also found in the perimysium surrounding muscle fiber bundles. Our previous studies showed that tenascin-C and collagen XII expression in primary fibroblasts is regulated by changes in tensile stress (Trächslin et al., *Exp. Cell Res.* 247: 320-328, 1999). We tested the hypothesis that tenascin-C and collagen XII expression in the connective tissue of skeletal muscle is modulated by increases in mechanical stress *in vivo*. Stretch (≥30% strain) of chicken anterior latissimus dorsi (ALD) muscle was accomplished by applying a load (10% of body weight) to the left wing, thus inducing hypertrophy. Stretch rapidly (within 36 hours) induced massive ectopic expression of tenascin-C (>10-fold) and collagen XII protein (>2-fold) in the space between single muscle fibres (endomysium) and around muscle fiber bundles (perimysium). Levels of tenascin-C and collagen XII in contralateral control ALD were not affected. Tenascin-C and collagen XII protein expression remained elevated until 7 days of stretch; it decreased within 5 days after release from 36 hours of stretch. In contrast, expression of ECM proteins laminin and tenascin-Y was not significantly changed by stretch of skeletal muscle. *In situ* hybridisation experiments indicated that mRNA coding for tenascin-C was induced uniformly in endomysial cells already after 4 hours of stretch. Our results imply that mechanical loading of skeletal muscle *in vivo* differentially controls expression of extracellular matrix proteins tenascin-C and collagen XII by direct activation of gene transcription in endomysial fibroblasts. They are consistent with a role of these ECM components during adaptation of adult skeletal muscle to mechanical stress, and they highlight our observations in culture. Future work will focus on elucidating the cellular and molecular mechanisms which selectively and reversibly control tenascin-C and collagen XII protein expression in response to tensile stress in vivo.

Analysis of a Stretch-Responsive Enhancer Region in the First Intron of the Chick Collagen XII Gene
Trächslin J., Mumenthaler U. and Chiquet M.

Recent evidence suggests that mechanical stress can directly affect transcription of specific ECM genes, such as for tenascin-C and for collagen type XII (see report by Flück et al.). In vitro, we showed that expression of the fibril-associated collagen XII is high when fibroblasts are attached to a stretched collagen I/III matrix, and low when they are cultured on a relaxed matrix, both on the mRNA and the protein level (Trächslin et al., *Exp. Cell Res*. 247: 320-328, 1999). Recently, we developed a device which allows to apply uniform biaxial stretch to

fibroblasts cultured on a ECM-coated silicon membrane. In first experiments, three impulses of 20% static stretch within 9 hours were sufficient to significantly increase the collagen XII mRNA level compared to the control, whereas the amount of fibronectin mRNA remained unchanged. This confirms in yet another system that collagen XII expression is specifically regulated by tensile stress.
To study transcriptional regulation of the chick collagen XII gene by mechanical signals, we cloned its 5'-region. By transient transfection of chick fibroblasts with promoter-reporter plasmids, we have reported previously that a highly conserved region in the first intron (600 bp) seemed to act as a mechano-responsive enhancer sequence (Chiquet et al., *Eur. J. Biochem*.. 257: 362-371, 1998). This intronic region contains a conserved DNA motif (GAGACC) which is found in the promoters of other genes induced by mechanical stress, such as the PDGF- and the tenascin-C promoter. Recently, we found that the central 200 base pairs of this region (which includes the GAGACC motif) retained the stretch-induced enhancer activity. Moreover, we could show that mutation of the GAGACC motif to GGATCC abolished the response of this enhancer region to mechanical tension.
In the case of the PDGF gene, it had been reported that a transcription factor of the NFκB family spcifically bound to the GAGACC sequence in its promoter. In a next step, we therefore investigated whether NFκB or a different nuclear factor recognized the GAGACC motif in the first intron of the collagen XII gene. Electrophoretic mobility shift assays (EMSA) were performed whereby a double-stranded (20-mer) oligonucleotide was radioactively labeled, incubated with fibroblast nuclear extract, and the resulting complexes electrophoresed on a native polyacrylamide gel. Indeed, a complex was formed between nuclear protein and the labeled GAGACC (but not the mutated GGATCC) motif from the collagen XII gene; this complex dissappeared upon competition with an excess of the same (unlabeled) oligonucleotide. In contrast, an NFκB consensus binding sequence did not interfere with the complex formed between nuclear protein and the collagen XII GAGACC sequence; conversely, unlabeled collagen XII GAGACC oligonucleotide did not compete with the binding of NFκB to its consensus sequence. Thus, we have to conclude that a nuclear factor different from NFκB (or at least of its isoforms studied here) binds to the mechano-responsive GAGACC motif in the first intron of the collagen XII gene; this factor(s) remains to be identified.

2.1.3 Tissue Biomechanics

Research in the Tissue Biomechanics area is directed at understanding the relationships between structure and function in conncective tissues, including cartilage, bone, ligament and tendon. The research emphasis lies in the role that physiologic and non-physiologic mechanical loading plays during musculoskeletal development, remodelling, disease and injury. Methodologies which are used by this research team span a wide range, including stereologic and histologic characterization of tissue microstructure, molecular and biochemical assays of connective tissue metabolism, and the measurement of tissue biophysical properties. These projects are being undertaken with a view to better understand the etiology of diseases such as osteoarthritis and to develop new therapeutic approaches for their treatment.

* * *

Stimulation of Aggrecan Synthesis in Cartilage Explants by Cyclic Loading Is Localized to Regions of High Interstitial Fluid Flow
Buschmann M.D., Kim Y.-J.K., Wong M., Frank E., Hunziker E.B. and Grodzinsky A.J.

Chondrogenesis in cartilage development and repair and cartilage degeneration in arthritis can be regulated by mechanical-load-induced physical factors such as tissue deformation, interstitial fluid flow and pressure, and electrical fields or streaming potentials. Previous animal and tissue explant studies have shown that time-varying dynamic tissue loading can increase the synthesis and deposition of matrix molecules in an amplitude-, frequency-, and spatially dependent manner. To provide information on the cell-level physical factors which may stimulate chondrocytes to increase production and export of aggrecan, the main proteoglycan component of the cartilage matrix, we characterized local changes in aggrecan synthesis within cyclically loaded tissue explant disks and compared those changes to values of predicted local physical factors. Aggrecan synthesis following a 23-h compression/radiolabel protocol was measured with a spatial resolution of ~ 0.1 mm across the 1.5-mm radius of explanted disks using a quantitative autoradiography method. A uniform stimulation of aggrecan synthesis was observed at an intermediate frequency of 0.01 Hz, while, at a higher frequency of 0.1 Hz, stimulation was only seen at peripheral radial positions. Profiles of radial solid matrix deformation and interstitial fluid pressure and velocity predicted to be occurring across the radius of the disk during sinusoidal loading were estimated using a composite poroelastic model. Tissue regions experiencing high interstitial fluid velocities corresponded to those displaying increased aggrecan synthesis. These results reinforce the role of load-induced flow of interstitial fluid in the stimulation of aggrecan production during dynamic loading of cartilage.

Biphasic Poroviscoelastic Simulation of the Unconfined Compression of Articular Cartilage - II: Simultaneous Prediction of Reaction Force and Lateral Displacement
DiSilvestro M.R., Zhu Q., Wong M., Jurvelin J.S and Suh J.-K.

This study investigated the ability of the linear biphasic poroelastic model (BPE), a linear viscoelastic solid model (LVE), and the linear biphasic poroviscoelastic (BPVE) model to simultaneously predict the reaction force and lateral displacement exhibited by articular cartilage during stress relaxation in unconfined compression. The BPE model assumes that the viscoelastic behavior of articular cartilage is solely governed by the fluid flow-dependent biphasic interaction between the interstitial fluid and the porous elastic solid matrix. The LVE model assumes that it is solely governed by the intrinsic viscoelastic nature of the solid matrix, independent of the interstitial fluid flow. The BPVE model assumes that it is governed by both the combination of both the fluid flow-dependent (biphasic) and fluid flow-independent (intrinsic) viscoelastic mechanisms of the tissue. It was found that the BPE model was able to accurately account for the lateral displacement, but unable to fit the short-term reaction force data of all specimens tested. The LVE model was able to account for the complete reaction force, but unable to fit the lateral displacement measured experimentally. The BPVE model was able to completely account for both lateral displacement and reaction force for all specimens tested. These results suggest that both the fluid flow-dependent and fluid flow-independent viscoelastic mechanisms are essential for a complete simulation of the viscoelastic phenomena of articular cartilage.

Mechanical Modulation of Tenascin-C and Collagen XII Expression During Avian Synovial Joint Formation
Mikic B., Wong M., Chiquet M. and Hunziker E.B.

The objective of this study was to investigate how temporal and spatial patterns of characteristic matrix molecules are altered in the absence of normal functional skeletal muscle contractions during avian synovial joint development. By using in situ detection of protein and mRNA expression in developing avian feet and knees from a wide range of developmental stages, we demonstrate that the morphological abnormalities which result from embryonic immobilization are associated with altered patterns of tenascin-C and collagen XII expression within developing joint structures. As the joints fuse in immobilized embryos, the cells of the presumptive articular surface differentiate from flattened fibroblasts to more rounded chondrocytes, and collagens XII and I are no longer detected at sites of complete joint fusion. While the expression of collagen XII persists at normal levels elsewhere within the immobilized joint, tenascin-C expression is diminished within the chondroepiphysis, synovium, and tendons, as well as within the remains of the fibrous articular surface. The effect is most notable for the shortest tenascin variant (Tn190) with the chondroepiphysis, and the largest variant (Tn 230) within tendons, synovium, and the fibrous surface layer of the joint. This study thus provides in vivo support of previous in vitro work which suggests that tenascin expression is sensitive to external changes in mechanical loading environment. However, these data do not support a similar conclusion for collagen XII in vivo.

The Biosynthetic Activity of Chondrocytes in Alginate Cultures
Wang X., Wong M. and Hunziker E.B.

The morphological characteristics, viability and proliferative capacity of bovine chondrocytes cultured in two types of alginate gel supplemented with different amounts of foetal calf serum were evaluated. The time course of matrix protein deposition within the extracellular space was followed by immunohistochemical methods. Ultrastructural features of the matrix were analysed by electron microscopy. The numerical density and proliferative capacity of chondrocytes increased progressively with time in culture, guluronic-acid-poor alginate gels being more conducive to both cell proliferation and matrix synthesis than guluronic-acid rich ones. Type II collagen and proteoglycan molecules were first detected in the extracellular space by day 7 and by day 21, a substantial matrix compartment – consisting of 67-nm cross-banded collagen fibrils and electron-dense granules representing proteoglycans – had been elaborated. No compartmentalization into pericellular and territorial regions was distinguishable in the electron microscope.

Volumetric Changes of Articular Cartilage During Stress Relaxation in Unconfined Compression
Wong M., Ponticiello M., Kovanen V. and Jurvelin J.

The time-dependent lateral expansion and load relaxation of cartilage cylinders subjected to unconfined compression were simultaneously recorded. These measurements were used to (1) test the assumption of incompressibility for articular cartilage, (2) measure the Poisson's ratio of articular cartilage in compression and (3) investigate the relationship between stress relaxation and volumetric change. Mechanical tests were performed on fetal, calf, and adult humeral head articular cartilage. The instantaneous Poisson's ratio of adult cartilage was 0.49 ± 0.08 (mean+SD), thus confirming the assumption of

incompressibility for this tissue. The instantaneous Poisson's ratio was significantly lower for calf (0.38±0.04) and fetal cartilage (0.36±0.04). The equilibrium Poisson's ratio was significantly higher for the adult tissue (0.26±0.11) compared to both the fetal (0.09±0.02) and calf (0.11±0.03) cartilage. A linear relationship between time-matched load and lateral expansion after the first minute of stress relaxation was observed.

Development of Mechanically Stable Alginate/Chondrocyte Constructs: Effects of Guluronic Acid Content and Matrix Synthesis
Wong M., Siegrist M., Wang X., Ahsan T. and Hunziker E.B.

The purpose of this study was to investigate factors which enhanced the compressive properties of alginate/chondrocyte constructs. Firstly, we studied the effect of biochemical composition and sterilization method on alginate properties. Secondly, we studied the biosynthetic characteristics of chondrocytes in three different alginate compositions and performed mechanical tests to determine whether the synthesis of cartilage matrix components could significantly enhance the compressive properties. 2% alginate solutions containing an initial cell density of $4x10^6$ cells/ml were cast into cylinders and cultured for 7 weeks. Compression tests, biochemistry, immunohistochemistry and electron microscopy were performed at fixed intervals during the seven-week culture period. The dynamic modulus, peak strain, and peak stress were maximum for alginate containing the highest percentage of guluronic acid. The high guluronic acid alginate, however, had significantly reduced matrix synthesis compared to alginate containing the lowest amount of guluronic acid. The presence of cells and their respective matrix components enhanced the equilibrium modulus of the constructs for all types of alginate, though this effect was small. The 1:1 mixture of the high and low guluronic acid alginates resulted in constructs which were both mechanically stable and which promoted synthesis of cartilage matrix proteins. In experiments and applications in which the mechanical integrity of the alginate is important, the composition and purity of the alginate and its method of sterilization should be selected with care.

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, 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.

* * *

Normal Skeletal Development of Mice Lacking Matrilin 1: Redundant Function of Matrilins in Cartilage?
Aszodi A., Bateman J.F., Hirsch E., Baranyi M., Hunziker E.B., Hauser N. Bösze Z. and Fässler R.

Matrilin 1, or cartilage matrix protein, is a member of a novel family of extracellular matrix proteins. To date, four members of the family have been identified but their biological role is unknown. Matrilin 1 and matrilin 3 are expressed in cartilage, while matrilin 2 and matrilin 4 are present in many tissues. Here we describe the generation and analysis of mice carrying a null mutation in the *Crtm* gene encoding matrilin 1. Anatomical and histological studies demonstrated normal development of homozygous mutant mice. Northern blot and biochemical analyses show no compensatory up-regulation of matrilin 2 or 3 in the cartilage of knockout mice. Although matrilin 1 interacts with the collagen II and aggrecan networks of cartilage, suggesting that it may play a role in cartilage tissue organization, studies of collagen extractability indicated that collagen fibril maturation and covalent cross-linking were unaffected by the absence of matrilin 1. Ultrastructural analysis did not reveal any abnormalties of matrix organization. These data suggest that matrilin 1 is not critically required for cartilage structure and function and that matrilin 1 and matrilin 3 may have functionally redundant roles.

Perlecan Maintains the Integrity of Cartilage and Some Basement Membranes
Costell M., Gustafsson E., Aszodi A., Mörgelin M., Bloch W., Hunziker E.B., Addicks K., Timpl R. and Fässler R.

Perlecan is a heparan sulfate proteoglycan that is expressed in all basement membranes (BMs), in cartilage and several other mesenchymal tissues during development. Perlecan binds growth factors and interacts with various extracellular matrix proteins and cell adhesion molecules. Homozygous mice with a null mutation in the perlecan gene exhibit normal formation of BMs. However, BMs deteriorate in regions with increased mechanical stress such as the contracting myocardium and the expanding brain vesicles showing that perlecan is crucial for maintaining BM integrity. As a consequence, small clefts are formed in the cardiac muscle leading to blood leakage into the pericardial cavity and an arrest of heart function. The defects in the BM separating the brain from the adjacent mesenchyme caused invasion of brain tissue into the overlaying ectoderm leading to abnormal expansion of neuroepithelium, neuronal ectopias and exencephaly. Finally, homozygotes developed a severe defect in cartilage, a tissue that lacks BMs. The chondrodysplasia is characterized by a reduction of the fibrillar collagen network, shortened collagen fibers and elevated expression of cartilage extracellular matrix genes, suggesting that perlecan protects cartilage extracellular matrix from degradation.

Hypertrophy of Growth Plate Chondrocytes In Vivo Is Accompanied by Modulations in the Activity State and Surface Area of their Cytoplasmic Organelles
Hunziker E.B., Kapfinger E. and Saager C.

The rate of longitudinal bone growth is regulated primarily by modulations in the activity of epiphyseal plate hypertrophic chondrocytes, these being manifested as changes in cell and matrix volume. It was the purpose of this study to ascertain whether the cytoplasmic organelles representing the cellular production apparatus, i.e. rough endoplasmic reticulum, Golgi apparatus and mitochondria, contribute to

these changes by modulating their rate of activity or by increasing/decreasing the surface area and/or volume of their membranes. Using rats at different stages of growth, the surface areas and volumes of the three organellar systems were quantified in epiphyseal plate chondrocytes at the onset and termination of hypertrophy by ultrastructural stereology. Matrix synthesis during the same span was assessed by monitoring the production of its principal components, namely, fibrillar collagen (ultrastructural morphometry) and glycosaminoglycans (quantitative ^{35}S-autoradiography). Each organelle adapts to increases (21- to 35-day-old rats) and decreases (35- to 80-day-old rats) in growth rate by its own individual combination of the two alternative mechanisms, but modulations in the level of activity predominate over alterations in the surface area or volume of their membranes. These findings point to the danger of relying solely on data gleaned from a quantitative ultrastructural analysis of organellar parameters and emphasize the necessity of conducting functional assays in parallel, as performed here.

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). Additionally, a Clinical Support Group (CSG) was established which consists of full-time orthopaedic surgeons (provided by the Department for Orthopaedic Surgery, Inselspital, Bern and the Semmelweis University of Medicine, Department of Orthopaedic Surgery, Budapest, Hungary) and medical students working on various projects.

In basic and clinical biomechanics, the major areas of focus are state of the art implant evaluations, musculoskeletal injury mechanisms and low back pain. Research methodologies in involve primarily *in vivo* and *in vitro* experimental work as well as mathematical (FE) models. The anatomic areas of interest are the spine, hip, and knee.

Research in the area of computer assisted surgery covers orthopaedic and ORL 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 http://www-mem.unibe.ch.

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2.2.1 Computer Assisted Surgery (CAS)

A-Mode Ultrasound as a Tool for Non-Invasive Registration
Amstutz C., Kowal J., Sati M. and Nolte L.-P.

This project proposes the use of an optically tracked A-mode ultrasound probe (called UltraPointer) for percutaneus registration of bone surface points.
In Computer Assisted Orthopaedic Surgery (CAOS), percutaneous non-invasive registration is potentially possible by ultrasound imaging. As compared to other ultrasound modalities, an A-mode probe offers several important advantages. With respect to integration into existing CAOS systems, it is similar to the

physically digitizing pointer used for invasive registration. Direct processing of the sampled signal provides real-time automatic bone surface detection. The technology adds less supplementary costs to an existing CAOS system as compared to B-mode. No expensive additional equipment is necessary. We therefore investigated the use of UltraPointer, a system based on an optically tracked A-mode ultrasound probe combined with a 3D user interface. The system allows detection of bony surface up to 80mm below the skin. Accuracy tests in water and on muscle specimens were performed. Registration was tested on tracked plastic bone models submersed in water, and on different extremity and spine cadaver specimen. For the cadaver tests, UltraPointer registration was compared to a golden standard provided by titanium fiducial marker screws. The accuracy of the ultrasound method is shown to be sufficient. Problems were imposed by propagation speed depending from soft tissue composition, high soft tissue attenuation, reflections from interfaces between different soft tissue structures, and weak reflection if the ultrasound beam is non-orthogonal to the bone surface. For depths up to several centimeters, UltraPointer allows non-invasive registration of bone surface points. Further clinical testing is required.

Restricted Surface Matching – Numerical Optimization and Technical Evaluation
Bächler R., Bunke H. and Nolte L.-P.

Accurate and reliable registration is one of the most important issues in computer aided surgery, as small errors may have a large influence on the overall accuracy of the system. The restricted surface matching algorithm (RSM), initially developed for the periacetabular osteotomy surgery (PAO), has been improved to become numerically more stable and reliable. To assess the accuracy and sensitivity of registration, a framework is presented, that evaluates two aspects of registration: (a) the sensitivity and raw performance of the registration algorithm is tested in a stand-alone environment, and (b) the integration into a CAS system is analyzed by evaluating the accuracy of the complete system. For the latter tests, spherically headed titanium screws used as fiducial landmarks provide a reference transformation for the registration. This framework was used to analyze the performance of RSM for the PAO. The sensitivity analysis showed the algorithm to be not sensitive to noise up to the magnitude of 3 mm. Both the sensitivity analysis and simulated surgical environment tests showed that an accuracy of better than 2 mm can be reached in the region of interest, and better than 4 mm far away from the region of interest. This is sufficient for safely assisting PAO surgeries.

Stencilled Fusion of CT and MRI Images
Bächler R., Hu Q. and Nolte L.-P.

To enhance the currently used CT images for CAS with respect to soft tissue representation, two methods have been explored. The first method consists of "blending" the two source image data sets by selecting, e.g., 60% of the CT and 40% of the MRI image. This will produce a new image containing the information from both modalities, and shows soft tissue structures if the MRI portion is ~40-60%. However, the whole image is not very convincing, as the image intensities of the original images are subdued. Therefore a second approach has been developed where the bony part of the image is cut out of the original CT (based on the segmented 3D bone model) and inserted as is into the fused image. The rest of the fused image is filled entirely with data from the MRI image by using an inversed cutting model. This approach has the advantage that the entire image content of the original images is preserved in the areas that are copied.

Bone and soft tissue structures are represented very clearly. This fusion method is referred to as "stencilled fusion". To allow the fusion of two image modalities they need to be co-registered. The current application for CT/MR image fusion uses a simple algorithm based on point pairs, that are required for the intraoperative navigation as well. The points were given by fiducial, self-adhesive skin markers that are CT and MRI compatible. However, this approach is limited in its accuracy by the low resolution that is normally used in MRI examinations. Further research areas include a semi-automatic registration method using surface data that is extracted from the CT and MRI modalities. The segmentation of the CT is quite straightforward and has been incorporated into the system from the beginning. To create a surface model of the MRI data set, the newly developed MRI segmentation algorithm could be used to provide the input for an existing surface based matching method. To improve the possibilities to modify the data set obtained by stencilled fusion, further research includes the evaluation of methods to adapt the image intensities in the original CT and MR images to enable, e.g., segmentation of the bone structures from the fused image data.

A Versatile Impingement Detection Algorithm
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 coherence 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 can perform impingement detection of two objects within 0.1 second. Experimental results concerning accuracy, reliability, and speed are given for a phantom and a patient's data set. Our 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.

Navigation of Acetabular and Pelvic-Ring Fractures
Hüfner T., Lawrence J., Tarte S., Langlotz F., Rosenthal H., Nolte L.-P. and Pohlemann T.

Routine preoperative analysis of acetabular fractures includes a CT, frequently with reformation and 3-D-views. However, intraoperatively the control of reduction is done with fluoroscopy or by direct visualization/digital. The aim of this study was to analyze the precision of a newly developed module for computer assisted surgery for pelvic-ring and acetabular fractures. A newly developed program which allows identification, registration and navigation of fragments was used. For real-time visualization of reduction the volume of the CT-datasets was reduced by generating surface models of the voxel data-sets.
For the analysis four set-ups were chosen for reduction: (1) Geometric blocks, (2) C1.2-Fracture with external fixateur at the fragments, (3) Displaced acetabular transverse fracture (Letournel). One experienced person in navigation performed

20 reduction maneuvers each using only the visualized objects on the screen while blinded to the real objects. Each trial was ended as soon as virtual reduction was completed. For a detailed evaluation the error of registration and verification and the result of reduction at defined landmarks (deviation in mm) were measured. For the geometric blocks, average steps after reduction were found to be 0.56 (0-1.7mm) in the horizontal plane and 1.77 (0-3mm) in the vertical plane. Average difference of distance at defined landmarks were 0,31 (0-4,3mm), and 1,9 (0,4-5,3mm), respectively. In the second trial the following deviations were recorded: symphysis 1.5 (0-4.3mm), SI-joint: 2.3 (0.5-4.2mm). In the test involving the acetabular fracture an average step/gap at 5 landmarks was found to be 0.51 (0-1.78mm). Within the joint these values were slightly bigger: 0.74 (0-1.92mm). Preliminary results reveal a high level of precision regarding fragment identification, surface model generation, registration and control of reduction. Metal artefacts did not affect the algorithm. Further improvements will include 2D reformations, surface registration and integration of instruments.

Computer-Aided Fracture Plate Fixation
Kowal J., Sati M., Bourquin Y., Rohrer U. and Nolte L.-P.

Minimal invasive surgical techniques for fracture fixation are difficult. The objective of the present study is to develop a system to improve the navigation of plate positioning and fixation during biological osteosynthesis. A fractured plastic bone, various osteosynthesis plates, a surgical drill, and screwdriver were instrumented with optoelectronic tracking markers. Two-dimensional (2D) X-ray images from fractured bone were integrated within a 3D OpenGL computer graphics environment. X-ray projection parameters were imported from another CAS system (Hofstetter et al., CAS, 4:65-76, 1999). A projection model determined from these parameters allowed display of detailed three-dimensional (3D) geometric models of surgical tools and implants overlaid onto the X-ray images. Optoelectronic tracking allowed the real time display of these objects within the scene. By scanning the plate surface, using a newly recently developed special slider tool, before surgical insertion, the system calculated the correct shape of the bent plate from a generic plate model. The system helps guide the surgeon to align the plate in the correct position relative to the underlying fracture site, drill the screw holes and insert the screws. The plate database is designed to be easily expandable to include new implants for future applications. 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. The reality enhancement provided by the 3D computer graphics overlay gives augmented perception of the implant orientation with respect to the underlying bone. The existing work shows that a minimal invasive fracture fixation could be improved using such a system. Replacement of constant fluoroscopy with a few computer-integrated X-ray promises significant reduction in radiation exposure.

Computer-Assisted Total Knee Arthroplasty
Kunz M., Sati M., Nolte L.-P., Strauss M., Ruether W. and Bernsmann K.

Some of the major mechanisms of failure in Total Knee Arthroplasty (TKA) are loosening and instability. The reasons can be misalignment of the prosthesis and stress on the components. To resolve this problem we develop a computer assisted total knee arthroplasty system. In contrast to current TKA instrumentation, CAS technology promises a reduction in the number of required hardware components. For tracking the motion of the knee patient references are attached to both femur and tibia. The first step of the system is the registration of the mechanical leg

axes. For registration of the hip center we use a special kind of pivoting algorithm, that does not require a reference base on the acetabelum. Femoral and tibial knee center and the ankle center are calculated based on specific points digitized at each joint and this method differs from that described in previous systems.
To avoid the stress to components, the system offers the possibility to intraoperatively navigate soft-tissue balancing. For this purpose the surgeon uses two mechanical clamps for holding both collateral ligaments under equal tension, before the first cut is performed. The computer calculates the gap in extension and flexion and gives the possibility to correct the planned cut with respect to the ligament behavior. To conserve the natural patellar-glide line, a joint line navigator is planned. It shows the distance between the natural and the planned knee joint line as a function of various virtually-planned femoral and tibial cuts (i.e. the plan is made before the cuts). After the complete virtual planning of all cuts the system navigates the surgeon to perform the planned cuts. A specially cut-guide equipped with optoelectronic markers, has been designed for this purpose. The proposed prototype solution gives the surgeon an overview of anatomical structures and soft-tissue behavior. This enables better solutions for total knee prosthesis placement.

Computer-Assisted Placement of a Double-Bundle ACL through 3D Fitting of a Statistically-Generated Template into Individual Knee Geometry
Sati M., Bourquin Y., Luites J.W.H., Blankevoort L. and Wymenga A.B.

This work describes the computer assisted implementation of a statistically-generated 3D anatomical template for double-bundle ACL placement. The implementation was based on a previously-developed computer assisted system for ACL replacement that allows real-time tracking of femur and tibia and interactive digitization and labeling of anatomical structures identified under direct visual or endoscopic control. The template has been previous generated through statistical shape analysis on a group of cadaver knees, mapped onto a cylinder and related to two major landmarks in the knee [Luites et al., CAOS 1999], namely the intercondylar notch surface and the cartilage border on the lateral wall of the notch. The interface was programmed in a wizard-like fashion guiding the surgeon through the steps of acquiring the required landmarks for the template alignment. The intercondylar notch surface was interactively digitized as a cloud of points using a computer-tracked palpation hook. An algorithm used this cloud of points to generate a 3D surface for better visualization. The same palpation hook was then used to interactively digitize the cartilage border. A cylinder fit into the notch surface through a Levenberg-Marquardt algorithm determined template orientation. The apex of the cartilage border curve as described in a cylindrical coordinate system found template rotation about the cylindrical axis. Since surgical orientation of the reference base on the femur is arbitrary, the system gave several different start conditions for the Levenberg-Marquardt algorithm and chose the solution having the smallest residual. The template was then visualized as a 3D cylinder for the user to verify proper algorithm convergence and suggested double tunnel locations were displayed as small 3D spheres. The computer interface was then used to guide a computer-tracked awl to the center between these points and the awl then used to mark the point with a physical indent. The CAS system was first tested on the population of knees that were used to define the template by comparing the anatomically marked bundle locations to those found by the numerical template fit. 34 femora were tested with the following differences in mm reported for the AMB and PLB bundle locations:
AMB: mean=3.2/sd=1.3/max=6.8/min=1.1 PLB: mean=2.1/sd=1.2/max=5.1/min=0.3 Algorithm convergence did not always give

the right solution on the first trial on each knee. In some knees the first digitization was enough, in some it needed to be redone several times. Refining of the notch surface with additional points until the cylinder fit was visually correct was possible for all knees. Even with several start conditions, total calculation time of the optimization algorithm was about 10-15 seconds on an Sun (Ultra 1 creator). The system was then used to position the insertion tunnels for a double-bundle procedure for a few cadaver knees.

2.2.2 Basic and Clinical Biomechanics (BCB)

Moment and Force Transmission in the Human Cervical Spine
Cripton P.A., Dumas G.A. and Nolte L.-P.

By virtue of the relative slenderness of the neck and the weight of the head, the cervical spine can be subjected to considerable loads. Knowledge about the basic biomechanics and load-sharing of the cervical spine may help to elucidate injury mechanisms or even suggest mechanisms leading to cervical joint degeneration. The aim of this study was to characterize the load transmission paths through cervical functional spinal units (FSUs). Compression and flexion, extension, lateral bending and torsional bending moments and anterior, posterior and lateral shear forces were applied. Under compression loading, the influence of superimposed flexion and extension posture was established. Under all other loading modes the effect of a constant axial preload was evaluated. The preload represented an active neck musculature and the weight of the head. An optoelectronic motion analysis system was used to measure specimen kinematics. Load-sharing mechanisms were measured using a miniature pressure sensor to measure intervertebral disc pressure and tri-axial strain gauges mounted beneath each of the facet joints and on the anterior surface of the vertebral body.
Our results suggest that flexion and compression flexion loading modes results in compressive force in the anterior column and tensile (or small compressive) forces in the posterior column. Extension moments resulted in compressive force at the posterior column and tension in the anterior column. Extension-compression caused compressive forces in the both anterior and posterior columns. Lateral bending moments were associated with higher loads in the facet towards which the segment rotated. Torsion moments caused equal loading at each of the facets. Under anterior shear the vertebra pivoted about the compressed annulus anteriorly and ramped up the facet joints posteriorly resulting in a net distraction of the intervertebral disc and decrease in disc pressure. Posterior shear resulted in a pure posterior translation tension at the anterior annulus and distraction of the facet joints. Lateral shear caused an impingement of the facet joint on the underlying lamina. These results identify which specific anatomic structure may be highly under each of the loads applied. Clinically, they can be used identify parts of the anatomy that should be examined for injury.

Cementless Fixation of Joint Prostheses with a New Concept Biomechanical and Clinical Aspects
Oetliker M., Orr T.E., Nolte L.-P. and Schawalder P.

Total hip arthroplasty is a common treatment for hip joint failure. The long-term success of this operation is hampered by several problems, particularly implant loosening and device-related osteoporosis. Implant loosening is caused by a breakdown of the bone-implant interface due to osteolysis, initiated primarily by wear particles. Implant related osteoporosis is caused by the remodelling of the femoral bone under conditions of low stress. The poor femoral bone quality is believed to adversely affect the results of revision surgery. To prevent implant loosening, attempts have been made to improve the bone-implant interface. The focus of this study is to design a new endoprosthesis utilizing a hollow, porous implant. The design rational is to have a new texture to produce better bone apposition. Further, the hollow design should allow better load transmission to the surrounding bone and thereby avoid the effects of stress shielding. The design goals of such an implant will be to achieve bony fixation into and through the implant to provide a better long-term fixation.
In order to test the new design, mechanical testing and an in vivo animal study is being performed. The new prototype was first designed as a canine hip replacement in order to prepare it for the clinical study. (The design will also be used clinically in canines since they also have severe hip damage.) The mechanical testing included determining the strength of the new implant (loading the implant to failure) and determining the fatigue characteristics of the new design. In addition, the primary stability of the new design implanted into canine cadaver bone will be determined. In order for this testing, a new three-dimensional sensor was developed based on the sensor developed in our institute for primary stability of human femoral stems. The sensor is based on eddy current transducers for measuring micromotion. The sensors have been designed so that they can be used in a clinical situation in order to measure the micromotions in vivo.
The results of the mechanical testing demonstrated that the new design had adequate ultimate and fatigue strength to withstand normal daily activities in the canine. The implant is now be prepared for the first clinical trial.

The Role of Facet Joints in Axial Torsion with and without Superimposed Extension/Flexion Moments
Orr T.E., Beutler T., Cripton P.A., Nolte L.-P. and Haberl H.

The role of the facet joint for load transfer in the lumber spine is still not well understood. Axial torsion is one of the most important loads since the facet joints play a significant role in resisting torque. The goal of this study was to further examine the role of the facet joint during axial rotation by determining the three dimensional kinematic response, including the analysis of the helical axis of motion and the influence of flexion-extension postures.
Eight human cadaveric lumbar spine specimens (levels L3-L5) were dissected into functional spinal units (FSU) and all surrounding non-ligamentous soft tissues were removed. Four aluminum spheres were glued to each vertebra and used as fiducial markers. The specimens were CT scanned with a reconstructed slice thickness of 1.0 mm. After the specimens were scanned, they were molded in PMMA blocks and mounted in a constraint-free spine machine. The following loading protocols were performed: pure axial rotation with no preload, axial rotation with a 200 N preload, axial rotation plus flexion or extension moments of 6 Nm induced by preload eccentricity. For each test, the axial rotation of 12.5 Nm was applied in 5 steps. The three-dimensional motions of the upper vertebra with respect to the lower vertebra was measured using an Optotrak motion

analysis system (Northern Digital, Waterloo, ON, Canada). The range of motion, the helical axis, and the instantaneous center of rotation were calculated for each load type and then animated using custom software. The vertebrae were segmented and reconstructed from the CT scans, and the CT-based model was matched to the experimental specimen through the digitizing of the aluminum spheres with a three-dimensional space pointer. Animation of the kinematic data, including the depiction of the helical axes of motion, allowed the visualization of the coupled motion during the moment application. The geometry of the facet joints for each specimen was examined for correlations with the motion behavior of the FSU. The axial rotation decreased by an average of 0.5 degrees when preload was applied. When additional flexion was applied, the range of motion decreased by an average of 0.4 degrees from the no preload case. When the specimen was in extension, the range of motion decreased by an average of 1.1 degrees. Although the majority of the specimens had the intersection of the helical axis in the posterior part of the verterbral body, there was no clear pattern for the different loading cases. In the majority of specimens, the helical axes did not not change between the no preload case and the preload case. Also, in the majority of the extension loads, there was no substantial coupling of lateral bending with rotation, whereas, coupling could be seen in several of the flexion cases. The average center of rotation moved posteriorly in extension. The specimens with a flattened facet joint geometry had greater range of motions.
This study demonstrated that the facet joints do play an important role in the overall kinematics of the spine. In flexion, the facet joints are not compressed; therefore, there was increased rotation during flexion compared to preload alone. However, during extension, the facet joints are compressed which decreased torsional range of motion. The compressed facet joints also restrict the movement so that there are few coupled movements other than the rotation. While the range of motion data was fairly consistent, the helical axes of motion was very variable and had no clear pattern. The differences in results could be explained by the individual facet joint geometry.

Factors Affecting the Behaviour of Interbody Cages in the Lumbar Spine: Finite Element Analyses
Polikeit A., Orr T.E. and Nolte L.-P.

Interbody cages in the lumbar spine have been a promising advancement in spinal fusion to relieve lower back pain. Experimental studies have investigated the influence of factors such as cage design, and vertebral bone density using three dimensional flexibility studies and compressive strength tests. The conclusions from these studies have shown that cage design is not as important a factor as the bone density of the adjacent vertebra. The objective of this study is to use the finite element method to investigate what factors have the greatest influence on the stresses in the vertebra.
Three-dimensional finite element models of a L2-L3 functional spinal unit (FSU) with and without an intervertebral cage were developed. The geometry of the model was based on reconstructed CT scans from a healthy cadaver specimen and consisted of 31716 elements for the intact case. This intact, ligamentous FSU model was validated by comparing resultant forces and strains to previously reported experimental studies. The design of the cage was based on the SynCage (Mathys Medical, Bettlach, Switzerland), but did not have such features as holes and teeth on the plates. Therefore, the elastic modulus of the material was reduced. An anterior approach was modelled. Contact elements with friction were used at the facet joints and the surfaces between the cage and the bone. Parametric analyses were performed varying the material properties of the cage (titanium, PEEK), the material properties of the adjacent bone (cortical, cancellous, endplate, posterior elements), and the loading conditions (pure

compression, off-axis loading). The material properties were obtained from the literature of previous finite element studies. The material property of cancellous bone was varied to represent those values of bone mineral density measured in previous spine studies. All models were compared with the corresponding intact model.
The insertion of the cage increased the maximum von Mises stress in all models and changed the load transfer in the adjacent structures. The variation of the cage material had much smaller influence than varying the properties of the underlying endplate and trabecular bone. In all cases, the stress in the trabecular bone on the periphery was less than in its corresponding intact model. The denser the cancellous bone, the more the stress was distributed underneath the cage while the peripheral structures were unloaded.
The finite element model in this study was based on physiological geometry, ligaments and material properties; however, there were some limitations. The homogenous, isotropic material properties simplified the real situation. Additionally, no annular tension due to the insertion was modelled, what might represent a worse case scenario. The altered load distribution may lead to bone remodelling of the vertebral structures and explain damage of the underlying bone. The results of this study agreed with previous experimental studies that suggest that density of the bone underneath the cage is one of the most important factors in determining the behaviour of the caged vertebra.

The Use of Facet Screws to Improve 3-D Flexibility of Interbody Cages: Comparison with Translaminar Screws
Szirtes B., Jensen L.M., Boos N., Nolte L.-P. and Orr T.E.

Recent studies have found that cages for anterior interbody fusion do not stabilise the spine in extension. The addition of translaminar screws significantly increased the stability of the construct. Translaminar screws have potential problems in contacting nerve structures in the foramen. The goal of the current study was to evaluate the feasibility of the Boucher method of screw fixation of the facet joints as a means to provide necessary stability. Seven human cadaveric lumbar FSUs were tested using a 3-D flexibility protocol. The flexibility test involved the application of unconstrained pure moments in flexion-extension, axial rotation, and lateral bending. The cage [SynCage®, Mathys Medical Ltd.] was inserted from an anterior direction. The screws used for the transfacet joint were AO cortical screws (22-26mm). The ranges of motion (ROM) were compared to the intact specimen for the cage alone and for the cage with facet screws. These ratios were then compared to a previous study that used the same protocol but with translaminar screws. The ratio of cage alone to intact ROM was similar to that of previous studies. The addition of transfacet joint screws increased the stability in all directions, with the exception of three specimens in extension. However, these exceptions may have been the result of poor bone quality.

Earlier investigations demonstrated that the addition of translaminar screws provided the necessary stabilization to anterior interbody cages. The use of transfacet joint screws demonstrated similar results. Transfacet joint screws may be easier to implant with less complications and have the theoretical potential to be inserted percutaneously with image guiding systems.

Stability and Strength of Tumor Replacement Constructs in the Cervical Spine: Biomechanical Study of New Cementing Technique
Ziems G., Frei H.P., Barden B., Nolte L.-P. and Orr T.E.

Vertebral body replacement with a bone cement plug has been proven means of restoring the spinal stability in patients with cervical vertebra which have been destroyed by malignant tumors. One problem with this technique is the post-operative instability at the bone/cement interface. The objective of this study is to determine if a new technique to create this cement plug will increase the stability of the new construct.
Twenty-four human cadaveric cervical segments (C4-C6) were corpectimized and four methods were used to restabilize. In two groups (n=6), a standard Palacos cement plug was placed between the C3 and C5 vertebra, with and without an anterior Caspar plate. In two other groups (n=6), a new method was implented to create a cement plug (also made from Palocos) that applied a vacuum to extract the bone cement into the underlying bone. This method was also tested with and without a Caspar plate. Three dimensional flexibility tests were performed and range of motions were measured before and after cyclic testing of 5'000 cycles.
The construct was more stable with the addition of the anterior plate for both cementing methods. The new technique of using a vacuum to create the cement plug resulted in a more stable construct than the traditional cement plug without the plate. This difference was significant in flexion where the cement plug's mean ROM was 15° and the vacuumed plug 's mean ROM was 2.2° (p=.016). There was no statistical difference in the results before and after cycling.
The new technique of using a vacuum to obtain better extraction of the cement into the bone interface demonstrates some potential. The new technique resulted in a more stable construct than the standard bone cement plug, although this was only statistically significant in the flexion direction.

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Book Articles

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Visarius H., Gong J., Scheer C., Nolte L.-P.: Man-machine interfaces in computer-assisted surgery. in: Computer Assisted Orthopedic Surgery (CAOS), L.-P. Nolte, R. Ganz. (eds), Hans Huber Publishers, Bern, Göttingen, Toronto, Seattle, 228-232, 1999

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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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Hunziker E.B.: Chondral defect repair in the goat using mesenchymal stem cells. Osiris Therapeutics, Baltimore, MD, USA 1.9.1999-31.3.2000

Langlotz F., Nolte L.-P.: Ein Head Mounted Display für Computerassistierte HNO-Chirurgie. University of Bern – Josephine Clark Fonds, Bern. 1.7.1999-1.8.1999

Nolte L.-P. Sati M., Bourquin Y.: Computer Assisted Knee Joint Replacement Based on the LCS Knee Systems, De Puy Orthopädie GmbH, Sulzbach, Germany. 1.9.1998-31.3.2000

Nolte L.-P. and Sati M.: Alternatives to CT-based computer assisted orthopaedic surgery. KTI, Kommission für Technologie und Innovation, Bundesamt für Konjunkturfragen, CH. 1.1.1998-31.12.2000

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. 1.10.1999-1.10.2002

Orr T.E., Jensen L., Szirtes B.: Pullout Characterization of Osteonics Spinal System Screws, Osteonics Inc.., Allendale, NJ, USA. 1.1.1999-1.9.1999

Orr T.E., Beutler T.: The effect of Facet Joint Geometry on Axial Rotation, Stryker, Inc., Raubling, Germany. 1.6.1999-1.4.2000

Orr T.E., Beutler T., Rojas M.: The pullout strength of dental implants with surface modifications in the mini-pig, Straumann, Switzerland. 1.7.1999-1.11.1999

Orr T.E., Beutler T.: The primary stability of cemented stems: an investigation of Stratec prosthetic designs, Stratec Medical, Oberdorf, Switzerland. 1.7.1999-31.12.2000

Orr T.E., Bellare A.: Assessing Deformation Mechanisms and Microdamage in Cortical Bone, Swiss National Science Foundation, Switzerland. 1.10.1999-1.10.2001

Pohlemann T., Langlotz F.: Computer assisted pelvic ring fracture fixation, AO/ASIF-Foundation, Bern. 1.12.1998-31.12.2000

Trueb B.: Transformation-sensitive Proteins of Tumor Cells. Swiss National Science Foundation, Bern. 1.10.1997-30.9.2000

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Wong M. and Hunziker E.B.: Effect of Repetitive Impact Loading on the Initiation of Osteoarthritic Changes in Articular Cartilage. Swiss National Science Foundation, Bern. 1.10.1996-31.1.2000

Wymenga A, Sati M., Stäubli H.U.: Two bundle anatomic anterior cruciate ligament reconstruction with computer assisted surgery, AO/ASIF-Foundation, Bern, 1.9.1998-30.9.1999

5 TEACHING ACTIVITIES

University of Basel:

- 2461 and 6525: New literature in extracellular matrix biology

University of Bern:

- Cytologisch-Histologisches Praktika für Medizin- und Tierarzt-Studenten im 1. Jahr.
- 4011: Coordinated lecture series in physics, chemistry, embryology, ecology, genetics, molecular biology, anatomy and psychology at the University of Bern
- S7364: Applied Molecular Biology, interfakultäre Vorlesung für Vorgerückte an der Universität Bern

Inselspital Bern:

- Biomechanics for Physiotherapists

Federal Institute of Technology, Zürich:

- 01-319: Kolloquium in Biochemie an der Abteilung XA

6 FELLOWSHIPS, DISSERTATIONS AND MASTER THESES

6.1 Dissertations Completed

Cripton, Peter A., Ph.D., Queen's University, Kingston, Canada, 1999
Load-Sharing in the Human Cervical Spine

Hofstetter R., Ph.D., University of Bern, Bern, 1999
Fluoroscopy Based Computer Assisted Surgical Navigation

Jaquemar D., Dr. Sc. Nat., ETH, Zürich, 1999
Characterization of a novel ankyrin-like protein with transmembrane domains that is lost after oncogenic transformation

Schmid P., Dr. med., University of Bern, Bern, 1999
Zellveränderungen und Synthesemuster von Matrixmolekülen in Chondrocyten-Agarose-Kulturen

7 HONORS AND AWARDS

1999 Trueb B.: Elected delegate of Switzerland by the Swiss Academy of Sciences at the assemblies of the International Union of Biochemistry and Molecular Biology for 2000-2003

03/1999 Best Poster Award, Computer Assisted Orthopaedic Surgery Congress, Davos, Switzerland, "Double Bundle Anatomical ACL Reconstruction with CAS Part I: Development of a 3D Femoral Template for Accurate Tunnel Placement: Wymenga A.B., Luites J., Blankevoort L,; vd Venne R., Sati M., Koolos J.G.M., Stäubli H.-U.

06/1999 Nolte L.-P.: Member of the Academic Council of the AO/ASIF-Foundation, Davos, Switzerland

8 GUEST PRESENTATIONS

8.1.1999 - Prof. Itzhak Binderman,: Transduction of mechanical stress in cultures of bone cells. School of Dental Medicine, Tel Aviv University, Tel Aviv, Jerusalem

19.1.99 - Andrew McIntosh, PhD Mechanics of Head Injuries in Sports. School of Safety Science, The University of New South Wales, Australia

26.2.1999 - Dr. Stefan Milz: Fibrocartilage in human tendons and ligaments. Anatomische Anstalt München, München, Germany

9.3.1999 - Dr. Paolo Giannoni: The extracellular fatty acid binding protein (ExFABP): a lipocalin involved in chondrocyte differentiation. Centro di Biotecnologie Avanzate, Genova, Italy

18.5.1999 - Drs Ivan Martin and Dirk Schaeffer: Alternative approaches to engineer autologous implants for articular cartilage repair. Chirurgisches Forschungslabor, Kantonsspital Basel, Basel

21.5.1999 - Drs Annemarie Moseley and Robert Deans: Mesenchymal stem cells: Culture to clinic. Osiris Therapeutics, Inc., Baltimore, USA

11.6.99 - Stephen Ferguson, M.Sc.E., Ph.D-Candidate: The Acetabular Labrum: Function in the Normal Hip Joint and Influence on Hip Joint Pathology. AO Research Institute, Davos, CH

15.6.1999 - Dr. Keld Ostergaard, M.D., Ph.D.: Histopathological classification of osteoarthritic articular cartilage. Institute for Inflammation Research, National University Hospital, Copenhagen, Denmark

28.6.99 - Prof. Michael Unser: Multiresolution splines and wavelets and their application for medical imaging. EPFL, Biomedical Imaging Group, Lausanne, CH

15.7.1999 - Dr. Suneel S. Apte, M.B.B.S., D.Phil.: Novel metalloproteases affecting extracellular matrix structure and function. Department of Biomedical Engineering (ND20), Lerner Research Institute, Cleveland Clinics, Cleveland, USA

26.7.1999 - Dr. Robert Schinagl: Depth-dependent compressive properties and cell adhesion in articular cartilage repair. Osiris Therapeutics, Inc., Baltimore, USA

23.9.1999 - Prof. Kathy Cheah, Ph.D.: Discovering genotype-phenotype relationships in chondrodysplasias. Department of Biochemistry, University of Hong Kong, Hong Kong

27.10.1999 - Prof. Mark Kachanov: Micromechanics of Porous Bodies with Applications to Natural and Artificial Biomaterials. Tufts University, Medford, MA, USA

2.11.1999 - Karl Kavalkovich, B.S.: Use of precommitted mesenchymal stem cells in an alginate construct for repair of a partial thickness chondral defect. Osiris Therapeutics, Inc., Baltimore, USA

2.12.1999 - Kelly Goodwin: The influence of functional strains on the lamellar properties of cortical bone. The Center for Locomotion Studies, The Pennsylvania State University, University Park, USA

17.12.1999 - Dr. Thomas Aigner: Gene expression profiling in human adult articular cartilage. Schwerpunkt Knorpelforschung - Osteoarthrose, Pathologisches Institut, Universität Erlangen-Nürnberg, Germany

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., PD	Deputy Division Head .....04.95 -
Chiquet Matthias, Ph.D. PD	Research Group Head (80%) ...05.95 -
Langlotz Frank, Ph.D	Research Group Head.....05.93 -

Orr Tracy, Ph.D.	Research Group Head	10.97 -
Sati Marwan, Ph.D.	Research Group Head	07.96 -
Studer Daniel, Ph.D.	Research Group Head (20%)	03.92 -
Wong Marcy, Ph.D.	Research Group Head (80%)	02.92 -

9.2 Research Associates

Allen Gregory, dipl. Ing.	Assistant	09.98 - 12.99
Ahsan Taby, Dr. Bio. Ing.	Postdoc	10.98 - 10.99
Amstutz Christoph, M.D.	Ph.D.-Student	01.99 -
Bächler Richard, dipl. Ing.	Ph.D.-Student	06.96 -
Belluoccio Daniele, dipl. Biol.	Ph.D.-Student	05.95 -
Berey Szilárd, M.D.	Assistant	10.99 -
Beutler Thomas, dipl. Ing. HTL	Assistant	05.99 -
Bourquin Yvan, dipl. Ing. HTL	Assistant	11.95 -
Brentnall Mark, dipl. Ing.	Exchange Student	07.99 -
Bugnon Véronique, dipl. Phil. II	Ph.D.-Student	03.99 -
Cao Xuesong, Dr. med., Dr. Phil.	Postdoc	07.98 - 02.99
Cripton Peter, dipl. Ing.	Ph.D.-Student	11.93 - 10.99
Driesang Iris, Dr. med.vet.	Assistant	06.96 -
Frei Hanspeter, dipl. Ing.	Assistant	05.94 - 06.99
Flück Martin, Dr. Phil Nat.	Postdoc	04.99 -
Giannoni Paolo, Dr. Phil.	Postdoc	04.99 -
Griessen Roland, dipl. Ing. HTL	Assistant	11.96 -
Hofstetter Robert, dipl. Ing.	Ph.D.-Student	06.96 - 09.99
Hoigné Dominik, cand. med.	M.D.-Student	10.99 - 12.99
Hu Qingmao, Dr. Ing.	Postdoc	10.97 -
Hunenbart Stefan, dipl. Ing.	Ph.D.-Student	09.99 -
Imhof Martin, dipl. Phil. II	Ph.D.-Student	01.96 -
Jaquemar Daniel, dipl. Natw. ETH	Ph.D.-Student	08.95 - 04.99
Jensen Laura, dipl. Ing.	Exchange Student	06.98 - 07.99
Kowal Jens, dipl. Ing.	Ph.D.-Student	10.97 -
Kubiak Monika, dipl. Inf.	Ph.D.-Student	11.99 -
Kunz Manuela, dipl. Inf.	Ph.D.-Student	06.98 -
Langlotz Ulrich, dipl. Ing..	Ph.D.-Student	07.96 -
Lawrence Jeffrey, M.Sc.	Assistant	04.97 - 12.99
Li Bo, dipl. Phil. II	Ph.D.-Student	06.99 -
Long Gong, Ph.D.	Postdoc	11.97 -
Oetliker Martina, cand. med. vet.	Ph.D.-Student	11.95 -
Polikeit Anne, dipl. Ing.	Ph.D.-Student	03.98 -
Rojas González Maricio, dipl. Ing.	Assistant	03.99 -
Schärer Nicolas, dipl. Ing. ETH	Ph.D.-Student	03.98 - 07.99
Schild Christof, dipl. Phil. II	Ph.D.-Student	06.99 -
Schmid Pirmin, cand. med.	M.D.-Student	09.96 - 01.99
Siegrist Mark, dipl. Phil. Nat.	Assistant	07.97 -
Szirtes Balazs, M.D.	Assistant	04.98 - 09.99
Tannast Moritz, cand. med.	Ph.D.-Student	08.99 - 12.99
Tarte Ségolène, dipl. Ing.	Ph.D.-Student	09.99 -
Trächslin Jonas, dipl. Phil. II	Ph.D.-Student	06.96 -
Wälti Heinz, dipl. Inf.	Assistant	12.96 -
Wang Xuanhui, med. Prakt.	M.D.-Student	08.98 - 12.99
Wiedemann Markus, dipl. Phil. II	Ph.D. Student	03.97 -
Yin Yunsheng, Prof. Dr. med.	Guest Professor	08.99 -
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 -	
Gnahoré Esther	Secretary (70%)	12.90 -	
Hutzli Walter	Aid Lab. Technician	11.89 -	
Kapfinger Eva	Res. Technologist (75%)	11.89 -	
Lüthi Marc	Apprentice in Fine Mechanics	08.99 -	
Mühlheim Erland	Mechanicien (50%)	01.92 -	
Mumenthaler Urs	Res. Technologist (80%)	06.95 -	07.99
Neseli Güler	Res. Technologist	08.96 -	
Neuenschwander Annelies	Secretary (35%)	04.95 -	
Perumbuli Prasanna	Res. Technologist	08.96 -	
Reist David	Res. Technologist	07.97 -	
Rohrer Urs	Head Mech. Workshop	07.91 -	
Schenker Thomas	Chief Technician	04.95 -	
Tunc-Civelek Vildan	Res. Technologist (80%)	09.99 -	
Walther Remo	Apprentice in Fine Mechanics	08.96 -	08.99

9.4 Scientific Consultant

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

10 MISCELLANEOUS

10.1 Conferences Organized

4th International CAOS Symposium, Davos, Switzerland, March 17-19, 1999

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
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- Prof. Dr. H. Reuter, Dept. of Pharmacology, University of Bern, Bern
- Prof. Dr. E.R. Weibel (Secretary and Vice President), M.E. Müller Foundation, Bern
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