WORKING GROUP 3. GENETIC ANOMALIES.
Chairpersons: K. Storhaug, A. Bloch-Zupan

12 May 2005

12h Keynote Lecture. Speaker: Prof Olivier COHEN: Collaborative Networks for the detection of genetic anomalies.

13h: **Chair: A Bloch-Zupan. Oral Communications**

13h' DELETION IN THE GENE ENCODING SPHINGOMYELIN PHOSPHODIESTERASE 3 (*SMPD3*) RESULTS IN *OSTEOGENESIS* AND *DENTINOGENESIS IMPERFECTA* IN THE *FRO/FRO* MOUSE
Opsahl S, Aubin I., Adams CP, Septier D, Bishop CE, Goldberg M, Poirier C, Guénet J-L

13h15' MOLECULAR BASIS OF MOST COMMON INHERITED CRANIOFACIAL DISORDERS
Adrianna Mostowska, Barbara Biedziak, Wieslaw H. Trzeciak

13h30' IDENTIFICATION OF GENETIC VARIATION IN MSX1, PAX9 AND AXIN2
Pekka Nieminen, Elina Luonsi, Sinikka Pirinen, and Sirpa Arte

13h45': GENOTYPE PROFILING OF SPORADIC ODONTOGENIC KERATOCYSTS
Heikinheimo K, Jee KJ, Morgan PR, Nagy B, Happonen R-P, Knuutila S and Leivo I

14 h: Lunch

15h30': **Oral Communications .Chair: Michel Goldberg .**

15H30' MUTATIONS IN DSPP GENE CAUSING DENTINOGENESIS IMPERFECTA TYPE II.
Richard B, Bloch-Zupan A, Lacombe D, Lopez-Cazeaux S, Till M, Verloes A, & Gorry P

15h45' MOLAR TOOTH PHENOTYPE REVEALED BY CASPASE 3 HOMOZYGOUS GENE DEFICIENCY
Matalová E , Lakhani S , Sharpe PT , Mísek I, Tucker AS

16h' MANAGEMENT OF THE PERIODONTAL DISEASE- REPORT ON ROMANIAN ONGOING CLINICAL STUDY FOR THE EVALUATION OF NEW, LOCAL IMMUNOSTIMULATORY PRODUCTS
Irina Codita, Adriana Radulescu, Dumitru Bungetzianu, Mariana Carmen Balotescu, Simona Radu, Mihaela Popa, Grigore Mihaescu

16h15': OSTEOBLAST GENE RESPONSES TO TITANIUM IMPLANT SURFACES
J. Harle, V. Salih, F.H. Jones, M. Tonetti, P. M. Brett .

16h30': MUTATIONAL ANALYSIS IN A GROUP OF OLIGODONTIA PATIENTS
Sirpa Arte, Pekka Nieminen, Laura Lammi, Lotta Veistinen, Sinikka Pirinen, and Irma Thesleff

16H45': FATE MAPPING OF THE DEVELOPING TOOTH GERM IN SLICE CULTURES
Abigail S. Tucker and Thimios Mitsiadis

18h : **Poster session. Chair: C Martínez-Álvarez**

- WG3: PHENOTYPING THE MUTANT MOUSE ORAL CAVITY
  J. Demassue, A. Hanauer, A. Bloch-Zupan

A. COLLECTING ORO-DENTAL PHENOTYPIC DATA: STANDARISATION AND NETWORKING VIA D[4]/ PHENODENT

A. Bloch-Zupan [1,2], J.C. Ennesser[1], A.M. Musset[1], M. Schmittbuhl[1], P. Ashley[2], S.Modi[4], P. Crawford[4], O. Cohen[3]

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The aims and objectives of the D[4]/ PHENODENT project are to create a collaborative interactive biomedical database D[4] (Diagnosing Dental Defects Database) linked to a dynamic web site PHENODENT allowing standardisation of data collection and therefore assisting in oro-dental phenotyping.

This tool will permit integration of these data within the medical and genetic general context enhancing multidisciplinary patient management approaches. It will facilitate understanding of dental and oral biology and associated disorders and diseases implementing science based evidence diagnosis and therapeutic options. These data might be used in public health as markers of gene/environment relationships in the case of acquired dental defects. D[4]/ PHENODENT will stimulate patient recruitment and install a basis for molecular analysis and anatomo-pathological investigations. It will allow the creation of larger cohorts of patients, presenting with these rare oro-dental defects, that could be involved in future research projects like - Oro-dental phenotypes in syndromes - Identification of mutations in known genes involved in dental development and diseases - Phenotype/genotype correlation - Population genetics – New gene identification - Gene expression during odontogenesis - Mouse/Human correlations. Standardisation will facilitate sharing of data and materials among investigators.

This tool will offer links to other genetic databases like Orphanet, OMIM, LDDB. It will be accessible via HC Forum ®, a secure web based platform dedicated to genetics.

PHENODENT will constitute a link between participating clinical diagnosis centres and research laboratories thus representing a powerful tool for national (French INSERM GIS rare diseases, Odontogenetics network) and international (European COST) networks.

This work is partially founded via INSERM « Reseau de Recherche Clinique et Reseaux de Recherche en Sante des populations 2003 » and COST-STSM-B23-00900.

DELETION IN THE GENE ENCODING SPHINGOMYELIN PHOSPHODIESTERASE 3 (*SMPD3*) RESULTS IN *OSTEOGENESIS* AND *DENTINOGENESIS IMPERFECTA* IN THE *FRO/FRO* MOUSE

Opsahl S[1], Aubin I.[2], Adams CP[3], Septier D[1], Bishop CE[3,4], Goldberg M[1], Poirier C[3,4], Guénet J-L[2]

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The recessive mouse mutation *fragilitas ossium* (fro) leads to a syndrome of severe *osteogenesis imperfecta* with no detectable collagen defect. The effects of the mutation are also detected in teeth. The size of the incisors, the density of the network of trabeculae in the alveolar bone, formation and mineralization in the dentin are clearly different in *fro/fro* and wild type mice. In the molar, dentine filled a residual pulp chamber, a situation close to some forms of *dentinogenesis imperfecta.*

Histochemical investigations were carried out on newborn mice, revealing with the von Kossa staining a reduced hypomineralization of alveolar bone and dentine in the *fro/fro.* This was correlated with an increased decorin and biglycan expression. A balance was detected between a decreased expression of DSP, and an increased expression of MEPE. Immunolabelling did not show any difference for MMP-2, -9 and -3. PCNA immunostaining was dramatically reduced in the *fro/fro* mouse, indicative of proliferation impairment, whereas no difference in cellular apoptosis was noted with the TUNEL technique. The lack of cell proliferation provides a clear-cut explanation for the differences of growth of the mutant teeth. Recently, positional cloning of the locus revealed a deletion in *Smpd3,* the gene coding for neutral sphingomyelin phosphodiesterase 3, truncating the encoded enzyme by one of its domains. As an intracellular enzyme, *Smpd3* is involved both in cell proliferation and in apoptosis. The effect on proliferation may be an indirect cause of the alterations seen in the *fro/fro* mouse. As an extracellular enzyme, *Smpd3* may be directly implicated in matrix sphingomyelin catabolism, a lipid found in dental tissues both as membrane- associated and mineral-associated matrix component.

Keywords: osteogenesis imperfecta, dentinogenesis imperfecta, neutral sphingomyelin, phosphodiesterasa

MOLECULAR BASIS OF MOST COMMON INHERITED CRANIOFACIAL DISORDERS

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Selective tooth agenesis and nonsyndromic cleft lip with or without cleft palate (CL/P) are the most common inherited craniofacial disorders in man. Despite this, little is known about the genetic defects responsible for these complex conditions. To date, many polymorphisms and several mutations correlated with these developmental malformations have been described. However, the results of the reported associations largely depend on the population and the geographical area of the world. The *MSX1, PAX9, TGFα* and *IRF6*, belong to the main candidate genes whose mutations are responsible for tooth agenesis, CL/P as well for the van der Woude Syndrome.
The aim of the project was analysis of main candidate genes responsible for tooth agenesis and orofacial clefts in a group of patients from the Polish population, in an attempt to explain the reason of these common developmental disorders.
The main results of the study of the candidate genes responsible for tooth agenesis were identification of three novel heterozygous mutations located in *MSX1* and *PAX9* that might be cause severe oligodontia. One of them, a 151A>G transition, found in a highly conserved *paired box* sequence of *PAX9* was the first *de novo* mutation described in this gene, suggesting that *PAX9* might be a good candidate gene for an isolated form of tooth agenesis.
Analysis of candidate genes responsible for orofacial clefting revealed an association between two polymorphic variants of *TGFα* (BamHI, OR = 1,878; RsaI, OR = 1,627) and cleft lip, with or without cleft palate, in a group of patients from the population tested. In opposition to other populations, it was shown that polymorphic variants of *MTHFR, IRF6, RARα* and *PAX9* were not associated with this common developmental disorder. The main result of this part of the project was the identification of a novel mutation in *IRF6* in a family with van der Woude Syndrome. This insertion (931ins T), located in the sequence encoding SMIR domain, might disturb the regulatory function of the encoded protein and result in an abnormal fusion of nasal and maxillary processes during embryogenesis.
The results of the investigations provide the first step to identification of genes contributing to the aetiology of selective tooth agenesis, as well as cleft lip with or without cleft palate in the Polish population, and might provide an insight into better diagnosis and prevention of these common inherited disorders.

Key words: tooth agenesis, orofacial clefts, *MSX1*, *PAX9*, *TRF6*, *MTHFR*

Acknowledgements: this work was supported by grant 2P05A 092 26 and the COST Action B23.

IDENTIFICATION OF GENETIC VARIATION IN MSX1, PAX9 AND AXIN2

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Genetic analysis has led to the identification of several mutations that cause severe tooth agenesis, oligodontia, or tooth agenesis associated with multiorgan syndromes. So far there is no data on mutations that comprise the background for hypodontia, the common type of tooth agenesis. It is plausible that sequence variants (mutations or common variants) in the same genes that cause severe tooth agenesis or syndromes may contribute to the common hypodontia, especially considering the apparently remarkable genetic heterogeneity of hypodontia. Sequence analysis of *MSX1*, *PAX9* and *AXIN2* has revealed several sequence variations in these genes. In most cases these represent polymorphisms (SNPs) as both alleles are rather common but in some cases the frequency of one allele appears to be relatively low. Only few of the variations cause amino acid changes in the proteins, and even in these cases it is possible that the change does not affect the function. The variations will be useful in linkage and association analyses to study the contribution of the genes to tooth agenesis. We have also used the known variations to construct haplotypes that segregate in the Finnish population. The identification of haplotypes helps to increase the power of association analyses and may help to reveal so far hidden sequence changes that affect the regulation of gene expression.

Keywords: hypodontia, polymorphism, mutation

GENOTYPE PROFILING OF SPORADIC ODONTOGENIC KERATOCYSTS

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The aim of the present study was to characterize the gene-expression profile and to detect possible gene aberrations at the DNA level in sporadic odontogenic keratocyst (OKC). For cDNA-array (Clontech Laboratories Inc), ten fresh-frozen OCK specimens and 20 pooled fetal tooth germs at the cap/bell stage were used. The results were complemented by quantitative real-time RT-PCR and immunohistochemistry. In addition, pooled DNA from five OKC samples was subjected to array-comparative genomic hybridization (aCGH; Agilent Technologies). A total of 106 genes were found to be dysregulated in OKC compared to the developing tooth. Several over-expressed genes were found to be located at 5q, 12q and several underexpressed genes at 17q. The over-expressed genes located on 12q included cytokeratin 6B (*KRT6B*), which was the most overexpressed gene (average of 10 fold) and epidermal- growth-factor gene family members (ERBB3 and HBEGF). Glioma associated oncogene homolog (*GLI1*), also located on 12q and known to be involved in the *SHH/PTCH* pathway dowstream, was also overexpressed. The results of aCGH analysis found an amplification in the 12q and deletion on chromosome 7. The results of the present study suggest that the over-expressed and amplified genes located in 12q may play an important role in OKC development and further that this cyst has a neoplastic nature.

MUTATIONS IN DSPP GENE CAUSING DENTINOGENESIS IMPERFECTA TYPE II.

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The human dentinogenesis imperfecta is an autosomal dominant disorder of the tooth that affects dentin biomineralisation. It is classified into 3 types based on clinical features (Shields). DGI-I is associated with osteogenesis imperfecta; DGI-II and DGI-III are restricted to the dentin. Another dentin defect is described as dentin dysplasia type II resembling DGI-II.
In the past, all of these human genetic diseases have been demonstrated to be allelic and mapped on the same locus on chromosome 4q21. Subsequently, DGI has been linked to mutations in the DSPP gene that consists of five exons spanning 16 kb localized on the chromosome 4(4q21.3). The DSSP gene encodes two major non collagenous dentin matrix proteins DSP and DPP.
Up to date, 10 mutations in the DSPP gene have been reported in families with DGI disorders around the world. Eight of them have been shown to cause DGI type II, one DGI-III and one dentin dysplasia. In addition, DSPP null mice have been shown to develop tooth defects similar to those seen in human DGI-III.
Through a French clinical network we undertook a DSPP mutations screening in families affected by dentinogenesis imperfecta. So far, we have screened 8 unrelated family cases. We successfully identified 5 new DSPP mutations as well some new polymorphisms. Clinical data and molecular results will be presented.. Criteria for clinical diagnosis, genotype-phenotype correlations, sensibility of the mutation screening, and DSPP structure-function correlations will be discuss in front of previous mutations reports, the evolution of DSSP sequence in mammals and the phenotype of DSPP KO mice.

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Keywords : dentinogenesis imperfecta, DSPP, genetic

Acknowledgements: Cost ActionB23 & INSERM « French network of odontogenesis ».

MOLAR TOOTH PHENOTYPE REVEALED BY CASPASE 3 HOMOZYGOUS GENE DEFICIENCY

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Caspases are a family of cysteine proteases acting as key effector molecules of apoptotis in mammalian cells. Caspases exist as zymogens and are activated in proteolytic steps during apoptotic intracellular machinery.

Caspase 3 deficiency leads to perinathal lethality (depending on mouse strain) due to neuronal hyperplasia and structural disorders. The caspase 3 knock-out on the B6 background gives viable mice up to few months. Tooth phenotype was investigated at the embryonic stage 15.5 to observe possible alterations particularly in the area of the enamel knots (EK). Apoptosis in the EK was shown to be involved in termination of these structures and may also have some morphogenetic role. Apoptosis in the EK was found to be caspase dependent, as general *ex vivo* inhibition of caspases in molar tooth buds led to persistence of the primary EK (PEK). Caspase 3 activation has been previously demonstrated in the primary EK of molar teeth using immunohistochemistry.

Serial sections of the head part of mutant and wild type embryos were analyzed by histological staining (haematoxylin-eosin) to evaluate morphological tooth germ alterations, by TUNEL test to detect apoptotic DNA breaks and by *in situ* hybridisation (ISH) of Shh and Fgf-4 to compare enamel knot marker expression in mutant and wt mice. Altered morphology was found in the EK area where the epithelial pit of the tooth bell (area of PEK) faced the mesenchyme in a multicuspid-like shape, in both, the upper and lower first molar tooth germs. Surprisingly, alterations were detected also in the cervical loops in the upper first molar. TUNEL assay has revealed no or very weak positivity in the entire orofacial region of the caspase 3 mutants. The absence of molecules downstream of caspase 3 prevents DNA cleavage and formation of apoptotic bodies as observed in the wild type. ISH of Shh molecules has not revealed any major changes in expression location, however, this was spread more widely into the inner dental epithelium and surrounding mesenchyme than in the wild type. Expression of Fgf-4 confirmed formation of secondary EK, however, its expression was not as clearly restricted in the mutant as in the wild type. This preliminary study will be followed by more detailed analyses and examination of the adult mutant tooth phenotype.

Up-stream molecules initiating caspase 3 activation during dental apoptosis have not yet been discovered. The interplay of growth factors and receptors as well as specific receptor mediated apoptosis may be involved in dental programmed cell death. Nevertheless, caspase 3 activation seems essential to perform apoptosis in the EK and to achieve the correct shape of the developing tooth germ.

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Key words: dental apoptosis, caspase 3, molar development

MANAGEMENT OF THE PERIODONTAL DISEASE- REPORT ON ROMANIAN ONGOING CLINICAL STUDY FOR THE EVALUATION OF NEW, LOCAL IMMUNOSTIMULATORY PRODUCTS

Irina Codita, Adriana Radulescu, Dumitru Bungetzianu, Mariana Carmen Balotescu, Simona Radu, Mihaela Popa, Grigore Mihaescu

We report here the evolution of our study concerning the clinical, microbiological and immunological evaluation of some new, local immunostimulatory methods used in the management of the periodontal disease.
Purposes: 1) selection of the patients for the constitution of the study groups based on clinical evaluation; microbiological characterization of the periodontal specimens prelevated from all patients before the beginning of the treatment; evaluation of the local and general immune status of the patients included in different study groups; starting with the administration of the proposed immunostimulatory products.
Population:
At present, three study groups are beginning to be outlined: 1) one control group constituted until now by 5 patients who came to the surgery and have been clinically and radiologically examined and submitted to local hygienization only; 2) one study group of 12 patients, who after the examination and local hygienization have received the local immunization with one of the tested immunostimulatory product represented by whole bacterial suspensions of standard density obtained from periodontal pocket anaerobic cultures; the product was given orally, sublingually in capsulated pharmaceutical form; 3) one study group of 11 patients with sterile pocket cultures who were immunized in the same way as the second group with whole, formaline-inactivated staphylococcal stock vaccine. All clinical, radiological, microbiological, biochemical and immunological parameters followed in this study have been noticed in a patient file.
Preliminary observations: Our results indicated a large diversity of the microbiota in different patients and the absence of any microorganism in few specimens. Concerning the immune status, abnormal values of IgM and C2 in patients with severe forms were noticed; the clinical evaluation of the patients taking the immunostimulatory product indicated the healing by gingival retraction, the reduction of gingival bleeding and teeth mobility and recovery of the normal gingival color. The post treatment microbiologic, biochemical and immunological parameters will be evaluated at three months after the end of the first administration.

Acknowledgement: This study was performed as part of Romanian participation on COST B 23 program which kindly offered the financial support for presentation of our results during this meeting.

OSTEOBLAST GENE RESPONSES TO TITANIUM IMPLANT SURFACES

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Previous studies have suggested that titanium implant surfaces of differing roughness or chemistries have marked effects on osseointegration *in vivo* and on osteoblasts (alveolar bone cells) *in vitro*. However, the molecular mechanisms underlying the surface-induced changes in osteoblast function are poorly understood.

Objectives: To examine the effects of different titanium surfaces on osteoblast morphology, attachment, proliferation and, most importantly, gene expression *in vitro.*

Bone cells were incubated for 3 and 24 h after attachment to four titanium surfaces; a smooth polished (SMO) titanium; a sandblasted and acid etched (SLA) surface; two ion implanted surfaces, one with calcium ions (CTi) and one with argon ions (ATi). SEM (scanning electron microscopy) was used to investigate morphology, ^{3}[H]-thymidine labelling to measure attachment and proliferation, and Affymetrix U133A 2.0 gene chips to determine the relative expression of approximately 18,500 genes. X-ray photoelectron spectrometry and SEM were used to characterize surface chemistry and roughness.

The osteoblasts showed different morphologies when cultured on the different Ti surfaces. High attachment rates were seen on all surfaces, but cells on SLA exhibited an initial poor spreading and growth rate compared to SMO. Gene profiling found pronounced differences in expression levels between surfaces. Genes with an apparent response to surface roughness were observed.

Conclusion: This study has shown that surface roughness and chemistry have a number of effects on osteoblasts including altered morphology, attachment, proliferation, and furthermore, these surfaces fundamentally alter gene expression. This suggests that improvements in the biological activity and clinical efficacy of Ti implants might be achieved by selective regulation of gene expression mediated via surfaces modifications.

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MUTATIONAL ANALYSIS IN A GROUP OF OLIGODONTIA PATIENTS

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Dominant mutations in transcription factors *MSX1* and *PAX9* have been described in nonsyndromic familial oligodontia. We have shown that oligodontia and predisposition to cancer are caused by a nonsense mutation in Wnt-signaling regulator *AXIN2*.

The aim of this study was to investigate the phenotypes and to screen mutations of *AXIN2*, *MSX1*, and *PAX9* in patients with severe tooth agenesis.

25 patients with missing of 6 or more permanent teeth were selected for the study. The patients were examined clinically and panoramic radiographs were taken. Information of general health and familial occurrence of tooth agenesis was obtained by interview. DNA was isolated from venous blood samples. For mutation screening, sequencing of *AXIN2*, *MSX1*, and *PAX9*-coding regions was performed.

Tooth agenesis was familial in 19 cases. The mean number of missing teeth was 12 (range 6 – 20), including third molars. Missing teeth were mostly premolars, upper lateral incisors, lower incisors, and molars. Some or all canines were lacking in six patients. Four patients had peg-shaped upper lateral incisors, two reported missing of upper primary lateral incisors. Two patients had juvenile idiopathic arthritis, six suffered from allergy, and two of lactose intolerance. In three families there were some cases of colorectal cancer. Even if the phenotypes of these tooth agenesis patients were similar to those described in *MSX1, PAX9,* and *AXIN2* mutations, we identified only one family with a mutation in *MSX1* and one patient with a mutation in *PAX9*. The mutation of *MSX1* was a novel mutation, causing a frame shift downstream of the homeobox. The *PAX9* mutation was similar to reported earlier in an unrelated Finnish family with oligodontia.

Keywords: oligodontia, phenotypes of tooth agenesis, mutation

FATE MAPPING OF THE DEVELOPING TOOTH GERM IN SLICE CULTURES

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The process of tooth morphogenesis is rather complex and our understanding of the process is hampered by the fact that as the tooth germ invaginates its subsequent development is concealed in traditional explant culture. Using a new technique, involving the dissection of the mandible into slices that can be cultured, we have been able to visualise the developing tooth, allowing previously unavailable access to the tooth germ in culture. The fate of cells in the tooth germ can then be followed by DiI labeling of different regions of the tooth germ. We have labeled groups of dental epithelial and mesenchymal cells using this technique and followed their movements from the bud to bell stage of development, a period when huge morphological changes are occurring. Using this technique the dynamic movement of cells and the shifting spatial relationship of the different cell types can be observed. We have started to map the early origins of regions that form distinct cell layers in the tooth (such as the inner dental epithelium and the stellate reticulum) and are in the process of trying to correlate such information with the restricted expression patterns of various genes, such as Tbx1. In this way cell lineage and specification can be inter-linked.

PHENOTYPING THE MUTANT MOUSE ORAL CAVITY (POSTER)

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Tooth development is under strict genetic control and involves continuous progressive inductive interactions between defined sites of the oral ectoderm and ectomesenchymal cells derived from the cephalic neural crest. Odontogenesis has been classically subdivided into several successive stages: dental lamina, bud, cap and bell stages, root formation and eruption. The location, identity, size and shape of teeth are determined during the early stages of tooth development. Differentiation of both odontoblasts and ameloblasts at the interface between epithelium and mesenchyme are also regulated by interactions between the two tissues, as well as the production of the dentine and enamel matrices. Disruptions of the involved signalling pathways and associated transcription factors lead to dental anomalies. Each dental abnormality: number, shape, size, structure, eruption corresponds to specific genetic and developmental issues. Hypodontia or missing teeth for example can be associated with the mechanisms of patterning of the dentition. These defects are seen in Human isolated dental genetic diseases (hypodontia, amelogenesis imperfecta, dentinogenesis imperfecta…) and in numerous syndromes in association with malformations of a variety of different organs. This is understandable as the genes regulating tooth development are used for the development of other body systems as well. Of the over 5000 genetic syndromes known more than 700 have dental/oral/craniofacial anomalies and over 250 have associated clefting. The mouse dentition seems to be a powerful and useful model to study the genesis of Human dental anomalies despite its intrinsic differences (monophyodontia, continuous growth of incisors, dental formula consisting of incisors and molars separated by a diastema). Analysis of the scientific literature demonstrates that the transgenic mice generated so far and displaying dental defects mimic the pathology encountered in Human in syndromic and non-syndromic situations. It is therefore important and relevant to record precisely and systematically the oral phenotype (OP) as part of the general phenotypical screen for mutant mice involved in the EUMORPHIA programme. EUMORPHIA is an integrated research programme involving the development of new approaches in phenotyping, mutagenesis and informatics leading to improve characterisation of mouse models for the understanding of human physiology and disease (see http://www.eumorphia.org/). The aims of this systematic oral phenotyping work is to define, validate and implement a standard screening protocol to monitor tooth development and homeostasis, to establish a test system that enables the investigator to discover mouse models for oral and dental defects and for genetic diseases affecting dental morphology and development (dentine and enamel formation), to develop new tests including NMR and CT for non invasive investigation of abnormalities in teeth, to propose a rational system for the classification of dental anomalies, to design a first-line screen for tooth defects, to establish a working baseline for the oral screening in the various strains of mice used. Examples of analysis of these transgenic mice are given: *rsk1, 2, 3* triple knockout (ribosomal S6 kinase family members) belonging to a group of X chromosomal genes in which defects cause unspecific mental retardation in human like Coffin-Lowry syndrome.

This phenotyping programme will be useful for the scientific community and especially for the scientists grouped under the European COST Action B23 Oral Facial Development.

Keywords: Teeth, odontogenesis, transgenic, mouse