Specific Support Action

Diagnostic Applications of Synchrotron Infrared Microspectroscopy

DASIM

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Diagnostic Applications of Synchrotron Infrared Microscpectroscopy
DASIM

Research topic addressed

LSH-2003-1.2.2-4: Advances in synchrotron radiation techniques for diagnostic purposes

Proposal abstract

The purpose of this proposal is to advance diagnostic applications of infrared microspectroscopy and functional imaging using synchrotron light sources.

Existing networks between biologists, clinicians and synchrotron scientists are already making impressive progress in IR microspectroscopy of cells and tissues leading to the identification of spectroscopic markers of diagnostic relevance. However, the European dimension is missing in these efforts because very few countries have synchrotron IR microspectroscopy facilities.

In order to further explore and advance the diagnostic possibilities of infrared microspectroscopy and imaging using synchrotron sources, there is a need to coordinate this research effort by networking the existing centers of excellence on the European scale and adding further necessary multidisciplinary expertise. This includes promotion of access to synchrotron facilities for experts from countries without their own facility, especially candidate countries.

Management aspects are important in this proposal, in order to avoid wastage through duplication of effort, to promote methodological validation by adding a multicentric quality control perspective, and thus to facilitate transfer of this emerging technology into clinical practice. To this end, we plan a disease-oriented, clinician-driven approach rather than a technology-driven approach.

The overall goal of the proposal and chief deliverable will be a report assessing the potential of synchrotron IR microspectroscopy for diagnosis on a per-disease basis, and making recommendations for further action in the sense of defining the future Framework Programme.

B.1 Objectives of the proposed project

The objective of the DASIM proposal is to coordinate, manage and disseminate international research effort in the characterization and classification of biological tissues and cells using synchrotron infrared microspectroscopy, in order to accelerate the application of this science for practical clinical diagnosis and to promote acceptance of the technique amongst the medical community.

In the last ten years there has been considerable progress in the application of infrared microspectroscopy to the analysis of human tissues in the context of disease diagnosis. It has been convincingly demonstrated in many studies that infrared spectroscopy can be used to classify tissues as normal or pathological. Comprehensive reviews of the field have been published recently by Jackson and Mantsch [1], by Dukor [2] and by McIntosh and Jackson [3]. The leaders in this field are (alphabetically) the groups of Diem (New York), Manfait (Reims), Mantsch (Winnipeg), McNaughton (Melbourne) and Naumann (Berlin). The two European groups are partners in the present proposal.

The central tool used in such studies is the infrared microscope, used for single point spectroscopy, for two-dimensional scanning and, more recently, for imaging with focal plane array detectors. The second essential tool is powerful statistical analysis, using techniques such as partial least squares, principal component analysis, cluster analysis and neuronal networks. When applied to spectral images of tissue specimens, such techniques reveal statistically significant spectral markers for the classification of tissues. On the basis of research experience to date, these techniques appear more promising for practical applications in diagnostics and pathology than the more conventional chemometrical approach of treating each spectrum as the sum of individually identifiable (bio)chemical components.

The special contribution that synchrotron infrared microscopy can make to this field lies in the up to 1000x higher brilliance (photon flux per unit source area and unit emission angle) of synchrotron light sources. Regardless of the light source, lateral resolution in infrared microspectroscopy is defined by the aperture used in the microscope, down to the diffraction limit of 0.61 λ/NA (in the case of a focal plane detector array, the pixel size is the aperture). The maximum photon flux that can be achieved through a given aperture size depends on the brilliance of the source. In practice, synchrotron light sources provide good spectral data at a lateral resolution less than the size of a single human cell, whereas with a conventional source an assembly of up to 1000 cells would need to be measured in order to achieve the same data quality. The latter approach would require that the assembly of cells is homogeneous and pure, which is not a realistic requirement for biological materials.

Thus synchrotron infrared microscopy remains the only practical way to obtain high quality spectra of individual cells from tissue and exfoliated cell samples in an acceptably short measuring time. This research input is essential for continuing progress in diagnostic uses of infrared spectroscopy, in order to achieve a fundamental understanding of the population diversity underlying the statistical findings described above, and to underpin the association between spectral markers and disease-related abnormalities with a sound fundamental understanding of the underlying biology. Only in this way will it be possible to develop reliable and secure algorithms for translating spectral data into diagnostic information in a form that clinicians can use.

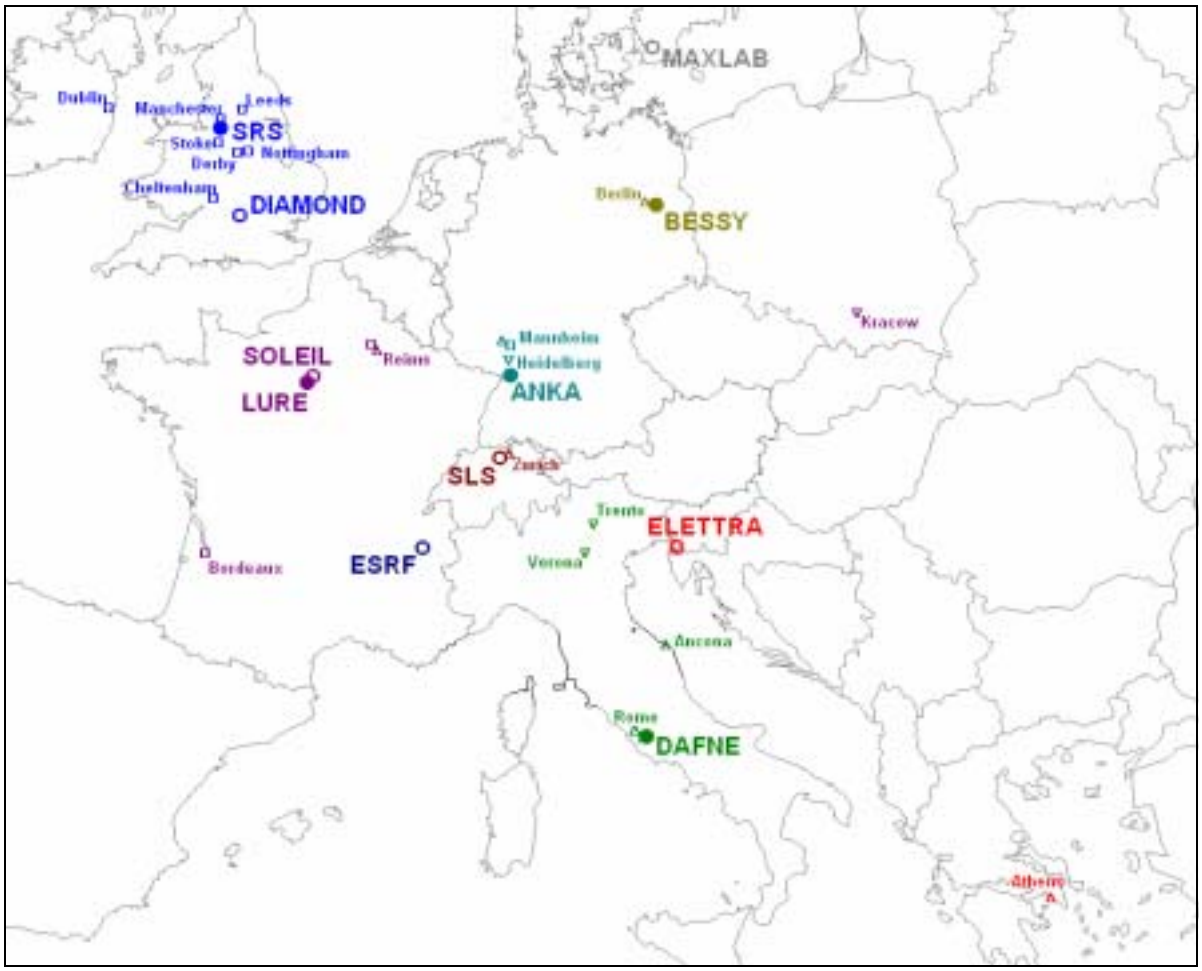
The first few published reports of synchrotron infrared microspectroscopy studies of cells and tissues have already appeared, and these have amply confirmed the capability of synchrotron infrared microscopy to obtain clinically relevant spectral information from tissues and cell cultures at the level of single cells [ca. 5 citations – Dumas 1998, Holman, Diem, Miller, Tobin].

Until very recently, Europe had synchrotron infrared beamlines only at Daresbury, Orsay and Lund. This compared very unfavourably with the situation in the USA, where NSLS Brookhaven alone has 6 infrared beamlines. However, three additional infrared beamlines were commissioned in the last twelve months at Frascati, Karlsruhe and Berlin, and further beamlines are under construction or in planning at Trieste, Zurich, Grenoble, Saclay and Didcot. This unprecedented development in the provision of synchrotron infrared light in Europe is driven by demand from scientific users from several fields, the biomedical field being one of the most prominent.

Each of these existing and planned synchrotron infrared light sources has attracted a local interdisciplinary consortium of beamline physicists, spectroscopists, biologists, pathologists and clinicians applying synchrotron infrared microspectroscopy to biomedical issues of direct relevance to clinical diagnostics. However, as yet there is essentially no coordination between these initiatives, which has very many negative consequences. There is much unnecessary duplication of effort, there is no standardization of procedures to facilitate comparison and pooling of results, there is no overall strategy to identify the most promising areas of application amongst the pool of indications being tackled, there is no mechanism to ensure that the synchrotron scientists and spectroscopists receive the same consensus input from the clinicians and biomedical scientists, there is no mechanism to ensure that each experiment is carried out at the technically most suitable beamline rather than simply the nearest, there is no strategy for a coordinated dissemination of the results to the medical profession... and so on. Within the framework of the FP6 SSA instrument, the DASIM group proposes to supply these missing coordination and management aspects on a pan-European scale.

The measurable and verifiable objectives of the DASIM proposal are:

- To organize meetings and workshops in order to coordinate and structure research effort in this field, to promote the exchange of ideas and formation of international research collaborations, to provide cross-disciplinary training, and to disseminate research findings to scientists, clinicians and industry.
- To disseminate a comprehensive account of the state of the art in this field by publication of a multi-author book in language understandable for all of the involved disciplines from physicists to clinicians.
- To disseminate research results especially to health care professionals via a ‘Virtual Knowledge Park’ that will provide a secure environment for the manage information and documents, for electronic structured discussion, and for mutual education and interactions between scientists from various fields, clinicians and other health care professionals.
- To produce a final report to the European Commission, presenting a realistic prognosis of the potential of this research field and specific recommendations for research funding in the future Framework Program



Synchroton Infrared Microspectroscopy in Europe – the need for coordination

This map shows the synchrotron infrared beamlines of Europe, with filled circles for facilities in operation and open circles for beamlines under construction or in planning. In addition, the map show the geographical location of the spectroscopists (Δ), biologists (▽) and clinicians (□) participating in the present proposal. The colour coding shows to which synchrotron facility these users have or are making contacts.

It is immediately apparent that independent local solutions are developing at the national or even regional level. There are only three instances where proposal participants from the user side have contacts with synchrotron facilities across national boundaries, and all three are from countries without their own synchrotron facility.

Also apparent is the uneven distribution of the different types of expertise required for diagnostic applications of synchrotron infrared microspectroscopy. The risk in this situation is that seemingly related research carried out at different synchrotron facilities is in fact incompatible, because the underlying expertise inputs are different.

The need for coordination at the European level is clear.

B.2 Relevance to the objectives of the LifeSciHealth Priority

The relevance of this proposal to research topic title LSH-2003-1.2.2-4 "Advances in synchrotron radiation techniques for diagnostic purposes" is self-evident and requires no further explanation.

However, one point that should be clarified is that we have interpreted this topic title as also covering advances in synchrotron IR microspectroscopy techniques which will ultimately lead to practical diagnostic applications that can be performed on standard laboratory IR microscope. While routine analysis of patient samples at synchrotron infrared beamlines may well be feasible for certain indications, it is clearly desirable wherever possible to transfer the techniques to instruments that can be placed in the hospital pathology laboratory.

The technical content objective for this research topic states: "*Medical research based on synchrotron radiation has already demonstrated high relevance in the diagnosis and treatment of major diseases. However additional coordination and structuring efforts are necessary to ensure this technology is used for future medical applications.*" Once again, the relevance of the coordination and structuring activities detailed in the present proposal is self-evident and needs no further explanation.

Turning to the relevance of the project objectives to the LifeSciHealth priority in general: diagnosis of disease is the basis for all clinical medicine. The primary requirement is reliability of diagnosis in order to ensure that therapies are appropriate and successful. However, the modern requirements of clinicians from diagnostic services go beyond a simple yes or no to the presence of a particular indication. Successful therapy requires information on disease subtype classification, assessment of the disease stage and extent such as the grading of tumours, as well as the monitoring of disease progress and therapeutic success. The speed of pathological analysis can also be amongst the requirements arising as a result of a time limited therapeutic window beyond which therapy may be less or no longer effective. Such constraints are particularly apparent in the treatment of cancer and infective diseases. Post-mortem diagnosis is also an aspect to be included, since there remain some diseases that can only be unequivocally diagnosed post mortem, and in these cases the retrospective diagnosis plays a central role in improving therapies through the accumulation of clinical experience.

Infrared microspectroscopy has proven capabilities for addressing many of these clinical requirements, so that the method shows considerable promise for making significant contributions to pathology, and thus to contribute to the LifeSciHealth objective "*to increase the possibilities and effectiveness of the existing therapies.*"

The introduction to the LifeSciHealth Work Program document states: "*In the field of applications, the emphasis will be put on research aimed at bringing basic knowledge through to the application stage ("translational" approach), to enable real and consistent and coordinated progress at European level in medicine and improve the quality of life.*" The objective of this proposal is to add a coordination and structuring layer to existing European research effort in the field of diagnostic applications of synchrotron infrared microscopy, in order to ensure that the true needs of clinical practice are addressed in the selection of research priorities, and in order to accelerate practical exploitation of this basic science by eliminating unnecessary duplication of effort and facilitating direct critical comparison of research results. These objectives directly address the aims stated in the above quotation.

At the wider societal level, the cost of medical care is an unavoidable issue. For diagnostics, the financial considerations include the capital and maintenance costs for instrumentation, the achievable working lifetime of the instrumentation, labour costs per analysis which is related in turn to the speed of analysis, the degree of expertise required and the amount of automation achievable, consumables and reagent costs as well as waste disposal costs for materials produced during the course of the analysis. On these issues, infrared microspectroscopy shows promise of being a cost-effective alternative. The method is by its nature associated with extremely low reagent consumption and waste production, very rapid analysis and an excellent potential for automation of sample handling and data interpretation. The capital equipment costs for infrared microspectroscopy are quite modest in comparison with many of the techniques recently introduced into medical care, and experience shows that such instrumentation has a relatively low maintenance requirement and an extremely long working lifetime. In cases where the analysis ultimately requires the brilliance advantage of a synchrotron light source and cannot be transferred to a benchtop instrument, the establishment of a dedicated beamline at an existing synchrotron as a regional service centre could also be achieved at costs that are by no means prohibitive and could well result in a cost saving in comparison with alternative methodologies. It can thus be concluded that the research field that this present proposal is far more likely to have a positive than a negative impact on health care costs.

A key aspect in maintaining relevance of a highly technical methodology to the LifeSciHealth priority is to ensure that the proposal is driven by “customer-side” clinical motivations and requirements, rather than technology driven. To this end, the clinicians consortium (participant 5) have been given a prominent role in the proposal management and are expected to take the lead in the definition of research priorities. This issue is related to the question of awareness of, education about and acceptance of new technologies by the medical profession, health professionals and patients, a theme explored in more detail in the following section.

B.3 Potential impact

The question of potential impact can be answered at two levels: (a) potential impact of the present proposal on the research field "diagnostics applications of synchrotron infrared microspectroscopy", and (b) potential impact of this research field on medicine.

The potential impact of the present proposal on the field of research targeted will be considerable. All of the significant players in the field in Europe are participants in the present proposal, as are all of the relevant European synchrotron radiation facilities. Therefore for the duration of DASIM, all diagnostics research at synchrotron infrared beamlines will be carried out within the DASIM framework. Through coordination and structuring of individual research efforts across the European synchrotron radiation facilities, a number of benefits will emerge as already detailed in Section B.1 – efficiency gains by elimination of duplication of effort, definition of standards to facilitate exchange and comparison of results, consensus building on the definition of the most promising lines of research as priorities, and inter-facility cooperation to ensure that each experiment is performed at the most suitable beamline. Probably the most significant benefits will arise from the extensive involvement of clinicians in the project, to provide high-value inputs concerning clinical requirements and expectations to all of the scientists involved, to ensure that such information input is the consensus opinion of representative leading clinicians across many fields of medicine, and to ensure that consensus information from the scientists flow back to the clinicians. It can be stated unequivocally that management and structuring of these activities at the European level is fundamental to achieving the most effective and progressive multidisciplinary research

Turning to the potential impact of the proposal on medicine, it is necessary to be more circumspect. As already shown in sections B.1 and B.2, infrared microspectroscopy certainly appears at this time to have the *potential* to become a key tool in diagnostics. It is equally clear that in spite of this promise, infrared microspectroscopy is not yet one of the tools used for diagnosis in health care. The question is, whether the potential of the technique will be realized, and whether it will win the acceptance of the medical profession. However strong the potential appears at this time, the sober assessment is that these questions at the moment are unanswerable, and indeed it is a central task and objective of the DASIM initiative to provide the answer to these questions by the end of the project.

To examine this issue in more detail: infrared spectroscopy is a powerful tool for characterizing the (bio-)chemical composition of a sample, but has very limited penetration depth. For this reason, except for certain special cases such as skin diseases, the position of infrared microspectroscopy within clinical diagnosis is at the level of *ex vivo* analysis of patient sample materials. This is certainly a serious limitation in the area of population screening for early detection and diagnosis, but it implies major contributions in the equally important areas of prognosis and therapeutic monitoring following disease detection. This puts infrared microspectroscopy into direct competition with traditional histopathology as performed by trained pathologists. The acceptance of this technique thus depends critically on targeting the actual needs of clinicians and pathologists – for example, do pathologists need a new tool in order to distinguish normal from malignant breast tissue? The answer is probably no. But there are many other questions that can be posed: would pathologists benefit from a tool that automates the elimination of definite negatives from a set of specimens, leaving more time for analysis of possible positives? Would pathologists benefit from a tool that can deliver reliable prognoses on the grade of a tumour and the likelihood of metastasis?

The potential impact of a new technology needs consideration in comparison with the strengths and weaknesses of existing methodology and practice. Cancer is assessed by histopathological examination. To achieve this, tissue is excised by the surgeon, fixed and sectioned and then stained, a time consuming and labour intensive process. Each section must be examined in detail by a specialist pathologist, whether or not it contains abnormal tissue. Practical and staffing constraints prevent a systematic analysis of the whole tumour and the specimen is sampled by taking sections at defined intervals, e.g. one section per cm, and/or additional sections at areas which are empirically considered on gross inspection of the specimen to relate to the tumour margin. Grading of tumour differentiation depends on the visual assessment of tissue architecture and characteristics of individual cells. Studies have shown only a 50% correlation in the reports of tumour differentiation, used as a prognostic indicator, between biopsy and definitive tumour resection specimens even when experienced pathologists have reported the material. The grading characteristics used are too subjective to allow a completely reliable interpretation using current techniques. Where such subjectivity carries over to cytological examination, as in the assessment of cervical smears, complete reliability cannot be achieved with unnecessary anxiety for some patients and missed pathology for others. Where invasion of bone may have occurred, decalcification is required before the tumour can be fully studied. This may take up to 6 weeks, by which time adjuvant radiotherapy should have commenced. To keep within the therapeutic window, doctors have to take decisions regarding an expensive treatment, which has both short and long term morbidity, without a full report on the disease they are trying to control. New technology is needed to assist pathologists in a demanding and important clinical area.

In microbiological diagnosis, specimens are taken, then cultured, a process requiring at least 24 hours. During that period the infection either continues unhindered or ‘best guess’ therapy is employed. Immediate characterisation of infective agents has key benefits as would any ability to predict therapeutic response to a given agent.

Infrared microspectroscopy can have a significant impact on clinical medicine if, and only if, it addresses the correct questions. By involving clinicians and placing them at the centre of the process of defining research priorities, the DASIM proposal seeks to ensure that this is the case and that those areas which can contribute most to clinical care are accorded priority.

Potential for commercial exploitation

Infrared microspectroscopy using synchrotron radiation has really only been developing in Europe for about five years, and the application of this in clinical diagnosis is even more recent. For this reason, the commercial potential of the this research has so far received minimal attention. The potential for commercial venture in this area can be divided into two main areas.

Firstly, interaction of the research community with equipment manufacturers aimed at advancing the current research capability. This level of exchange is already beginning to occur, for example between synchrotron facilities and major FTIR manufacturers, and between research groups and designers of dedicated FTIR instrumentation targeted at the bioscience research sector. However, interaction generally happens on a local basis. By promoting wider co-operation between multiple user groups and synchrotron providers with engineering companies, the development of analysis software, instrumentation such as sample chambers, and other specialised FTIR peripherals with wider applicability will be achieved. It

is in this area that most commercial involvement is expected to occur during the lifetime of the programme.

The second area of commercial potential is the opportunity to transfer the knowledge and technology to a working clinical environment, such as a pathology laboratory, in the form of a dedicated instrument. We do not see this exploitation as an aim of this Programme, since the belief is that the technique still requires proof of principle, but the Programme's outcomes may facilitate this in the future.

We propose to facilitate commercial interaction by several means. These will include:

- Involvement of relevant companies in the annual DASIM workshops. Representatives of research programmes in which there have been considerable involvement of commercial companies will be invited to present their work.
- Where relevant, individual Workgroups will be given the task of evaluating the potential of specific opportunities involving interaction with commercial companies, e.g. in software development or evaluation.
- Intellectual Property protection will require specific consideration by the workgroups where interaction with external businesses is likely. Where many different laboratories are involved, the Virtual Knowledge Park will act as a link between the researchers and commercial departments of each of these laboratories.
- The potential for translation of IR spectroscopy to the clinical environment will be the study area of a Workgroup at a later stage of the programme. Consideration of the possibilities for subsequent collaboration with commercial companies in areas of instrument development will be made at this stage.

B.4 The consortium and project resources

The DASIM consortium consists of five participants. Participant 1 is the Proposal Coordinator, the other four are teams representing the central areas of expertise necessary for this highly interdisciplinary research field. Participant 2, the synchrotron physicists team, are the providers of synchrotron radiation and all the facilities necessary for carrying out measurements at synchrotron facilities. The group includes the infrared beamline scientists at all existing and planned synchrotron facilities in Europe. Participant 3, the spectroscopists team, bring in the expertise and experience concerning sample preparation, spectral data acquisition and statistical interpretation. This team includes some of the worldwide leaders in the field of diagnostic application of IR microspectroscopy using benchtop instruments. Participant 4, the biologists team, is responsible for providing the required know-how on cell biology, cell and tissue culture techniques and relevant established reference methods such as fluorescence microscopy. Participant 5, the clinicians team, takes the lead in the definition of research priorities according to the needs of health care practice, provides patient sample materials and provides reference diagnostic information.

PARTICIPANT 1 – PROPOSAL COORDINATOR
David Moss (Karlsruhe, Germany)

The proposal coordinator is the infrared beamline scientist responsible for biomedical applications at the ANKA synchrotron radiation facility of the Forschungszentrum Karlsruhe in Germany. He was appointed to a permanent position as a staff scientist at the Forschungszentrum Karlsruhe in 1990, after completing his Ph.D. in Biochemistry at the University of Cambridge and postdoctoral work in Biophysics at the University of Freiburg, Germany. He has 16 years of experience in the field of biomolecular applications of infrared spectroscopy, and has won international recognition particularly for his contributions to experimental methodologies in this field. He has conceived and supervised 13 student research projects in this field, including doctoral work that was awarded the Perkin-Elmer Prize for "outstanding scientific achievement in the field of instrumental analysis in environment and medicine" in 1996. Of his currently active research projects, the most relevant to the present proposal is a study of the dynamics of single living human cancer cells in culture using synchrotron infrared microspectroscopy, in collaboration with EMBL Heidelberg.

He was selected unanimously by the proposal participants to act as Coordinator because of his range of expertise covering the areas represented by Participants 2, 3 and 4, because of his long-standing personal contacts and familiarity with the work of many of the individuals participating in the proposal, and because of his proven organizational and management abilities, in particular in the organization and chairmanship of the "1st Workshop on Biological Applications of Synchrotron Infrared in Europe" in September 2003.

Recent relevant publications:

F. Sokolowski, A. J. Modler, R. Masuch, D. Zirwer, M. Baier, G. Lutsch, D. A. Moss, K. Gast and D. Naumann, "Formation of critical oligomers is a key event during conformational transition of recombinant Syrian hamster prion protein", *J. Biol. Chem.* (in press)

M. Keese, R. Pepperkok, and D. A. Moss, "Synchrotron IR spectroscopy of single living human cells at ANKA-IR", *1st Workshop on Biological Applications of Synchrotron Infrared in Europe*, Kalrsruhe, 11-12 September, 2003

R. Masuch and D. A. Moss, "Stopped flow apparatus for time-resolved FT-IR difference spectroscopy of biological macromolecules in $^{1}H_2O$", *Appl. Spectrosc.* **57**, 1407-1418, 2003

Y.-L. Mathis, B. Gasharova and D. A. Moss, "Terahertz radiation at ANKA, the new synchrotron light source in Karlsruhe", *J. Biol. Phys.* **29**, 313-318, 2003

Moss, D.A. and Mathis, Y.-L., "Infrared imaging at diffraction-limited spatial resolution with ANKA, the new synchrotron light source in Karlsruhe", *Shedding New Light On Disease*, Reims, France, June 23-27, 2002

PARTICIPANT 2 – SYNCHROTRONS
Team Coordinator: Augusto Marcelli (Frascati, Italy)

This node gathered the physicists, chemists and biologists (listed below) who are in charge for all the infrared synchrotron facilities, either operational or under construction in Europe: ANKA, BESSY, DAFNE, ELETTRA, ESRF, LURE, MAX, SLS, SOLEIL, SRS, DIAMOND and MAXLAB. In the past years, the demand for the use of synchrotron-based infrared microspectroscopy to improve diagnostic applications and functional imaging significantly increased. Remarkable results have been already achieved thanks to the existing instrumentation. However, it is necessary to coordinate the research effort by networking on the European scale the existing centers of excellence to face this new scenario. The main tasks of the team will be: i) publicizing the potential of infrared synchrotron radiation in clinical diagnostics; ii) promoting the access of European users to the facilities; iii) improving and adapting the technology of synchrotron instrumentation to the needs of clinical diagnostics.

Name	Position	Affiliation	Relevant expertise
Augusto Marcelli	IR beamline scientist	DAFNE synchrotron facility, Frascati, Italy	Synchrotron radiation instrumentations, sources and detectors; Infrared spectroscopy on biological systems.
Paolo Calvani	Professor of Physics	Department of Physics, University of Rome 'La Sapienza', Italy	Study and applications of infrared synchrotron radiation; Responsible for IR microscopy instrumentation at DAFNE
Mike Chesters	Director of the facility	SRS synchrotron facility, Daresbury, UK	Infrared microspectroscopy of cervical and oral cancer; Responsible for new IR microscopy facility at DIAMOND
Leonardo Degiorgi	Assistant Professor	Laboratory of Solid State Physics, ETH Zurich, Switzerland	Responsible for new IR microspectroscopy instrumentation at SLS
Paul Dumas	IR beamline scientist	LURE synchrotron facility, Orsay, France	High resolution imaging of individual cells and human tissues; Responsible for new IR microscopy facility at SOLEIL
Karsten Hinrichs		Insitute for Spectrochemistry and Applied Spectroscopy, Berlin	Responsible for the infrared ellipsometry station at BESSY
Yves-Laurent Mathis	IR beamline scientist	ANKA synchrotron facility, Karlsruhe, Germany	Development and application of infrared synchrotron-based sources
Stefano Lupi	Senior researcher	Department of Physics, University of Rome 'La Sapienza', Italy	Responsible for the IR experimental station of the University La Sapienza at ELETTRA
Bengt Nelander	IR beamline scientist	MAX-lab synchrotron facility, University of Lund, Sweden	Responsible for the existing far IR and the new IR microspectroscopy beamline at MAXLAB

Luca Quaroni	IR beamline scientist	Elettra synchrotron facility, Trieste, Italy	Membrane Biochemistry, Biophyisics, Enzyme kinetics, Microscopy
Pascale Roy	IR beamline scientist	LURE synchrotron facility, Orsay, France	Functional study of proteins by IR and Far IR spectroscopies. Study of water in biological systems by IR and Far IR spectroscopies
Muriel Salomé	X-ray and IR beamline scientist	ESRF, Grenoble, France	Bone chemistry; Microscopy image processing
Ulrich Schade	IR beamline scientist	BESSY synchrotron facility, Berlin, Germany	Synchrotron near- and mid-infrared, spectroscopy and microspectroscopy; Mid-infrared spectroscopic ellipsometry; THz spectroscopy
Jean Susini	X-ray and IR beamline scientist	ESRF, Grenoble, France	Elemental and chemical analysis applied to biology
Mark Tobin	IR beamline scientist	SRS synchrotron facility, Daresbury, UK	IR spectroscopy of malignant invasion in cancer; Live cell spectroscopy
Per Uvdal	IR beamline scientist	MAXLAB synchrotron facility, University of Lund, Sweden	Responsible for new IR microspectroscopy beamline at MAXLAB
Jörg Wambach	IR beamline scientist	SLS synchrotron facility, Villigen, Switzerland	Responsible for new IR microspectroscopy beamline at SLS

Recent relevant publications:

Y-L. Mathis, P. Roy, B. Tremblay, A. Nucara, S. Lupi, P. Calvani, and A. Gerschel, "Magnetic field discontinuity as a new brighter source of infrared synchrotron radiation", *Phys. Rev. Lett.* **80**, 1220 (1998)

Abo-Bakr, J. Feikes, K. Holldack, H.-W. Hübers, U. Schade, G. Wüstefeld, "Powerful, Steady State, Coherent Synchrotron Radiation at BESSY II", *European Particle Accelerator Conference (EPAC)*, 3.-7. June 2002, Proceedings, 778-780 (2002)

Moss, D.A. and Mathis, Y.-L. "Infrared imaging at diffraction-limited spatial resolution with ANKA, the new synchrotron light source in Kalrsruhe", *Shedding New Light On Disease*, Reims, France, June 23-27, 2002

L. Bozec, A. Hammiche, M. J. Tobin, J. M. Chalmers, N. J. Everall and H. M. Pollock "Near-field photothermal Fourier transform infrared spectroscopy using synchrotron radiation", Meas. Sci. Technol. 13 1217-1222 (2002).

P. Dumas and G.P. Williams, in: Chemical Applications of Synchrotron Radiation, Advanced Series in Physical Chemistry, World Scientific, 12 (2001)

PARTICIPANT 3 – SPECTROSCOPISTS
Team Coordinator: Michel Manfait (Reims, France)

In recent years, the spectroscopy/imaging and medical communities have witnessed an ever-closer relationship due to the need of novel methods that can provide new diagnostic capabilities for research applications and to physicians directly implicated in patient treatment. New techniques have emerged and old techniques have been adapted to face the challenges set in developing diagnostic and clinical applications of optical techniques. Infrared synchrotron micro-spectroscopy is one such technique that has progressed in view of fulfilling such demands. Its high brilliance beam, high spatial and energetic resolution, give access to spatially resolved bio-chemical information from various bio-molecules in their natural environment without harming the studied system or perturbing it with the addition of extrinsic labelling or staining. It allows generation of high-fidelity spectroscopic information and spectral images useful for diagnostic purposes alongside conventional optical images. In this quest for optically-based diagnostic solutions, the eclectic blend of scientists including biologists, physicists, physical chemists, statisticians, and physicians, involved in this node,

will join forces to tackle issues in medical sciences such as phenotypic characterisation of cells, tissues and micro-organisms, host-cell/parasite and host-cell/HPV interactions and bone analysis.

Name	Position	Affiliation	Relevant expertise
Michel Manfait	Professor	Pharmacy Dept., University of Reims, France	FTIR and Raman spectroscopy of living cells and tissues, early diagnosis and prognosis in cancer pathology
Ganesh D. Sockalingum	Assistant Professor	Pharmacy Dept., University of Reims, France	Vibrational spectroscopy and imaging of cells and tissues, early diagnosis and prognosis in cancer pathology; Microbial characterisation
Dieter Naumann	Professor	Robert-Koch-Institut, Berlin	Biomedical IR spectroscopy of microorganisms; Structural IR spectroscopy
Peter Lasch	Research Scientist	Robert-Koch-Institut, Berlin, Germany	Biomedical IR spectroscopy of tissues, bio-fluids, eucaryotic cells; MALDI-TOF spectroscopy; Chemometrics
Heinz Fabian	Research Scientist	Robert-Koch-Institut, Berlin, Germany	Biomedical IR spectroscopy of tissues, eucaryotic cells, bio-fluids; Structural IR spectroscopy; Protein structure and folding; Nucleic acids
Agostina Congiu Castellano	Associate Professor of Biophysics Laboratory	Department of Physics, University of Rome 'La Sapienza', Italy	Investigation of apoptosis and necrosis of cells with IR spectroscopy
Silvia Gaudenzi	Research Scientist	Department of Physics, University of Rome 'La Sapienza', Italy	Investigation of apoptosis and cecrosis of cells with IR spectroscopy
Paolo Mariani	Associate Professor of Physics	Polytechnic University of Marche, Ancona, Italy	Structural properties of biomolecules; Protein folding/unfolding; Protein structure determination by spectroscopic techniques
Francesco Spinozzi	Contract researcher in Biophysics	Polytechnic University of Marche, Ancona, Italy	Protein structure determination by computational prediction techniques
Giorgio Tosi	Professor of Physical Chemistry	Polytechnic University of Marche, Ancona, Italy	IR microspectroscopy of cells in cultures and tissues
Gérard Déléris	Professor of Bio-Organic Chemistry	University of Bordeaux, France	Analytical and biochemical investigations with FT-IR spectrometry and imaging; Synthesis of biomarkers for IR and PET imaging.
Cyril Petibois	Research Scientist	University of Bordeaux, France	Analytical and biochemical investigations with FT-IR spectrometry and imaging.
Jürgen Backhaus	Professor and Head of Institute	Institute of Instrumental Analysis, University of Applied Sciences, Mannheim, Germany	NIR and IR spectroscopy as tools for clinical diagnosis
Hugh Byrne	Research Facilities Manager	Dublin Institute of Technology, Ireland	Applications of spectroscopy, optical and electronic properties of molecular and biological material
John Chalmers	Consultant in Spectroscopic Analysis	CCLRC Daresbury Laboratories, UK	Analysis and software development for analysis of biological (especially human tissue and cell) spectra.

Recent relevant publications:

M. Manfait and G. D. Sockalingum, "Method of identification of a functional biological characteristic of living matter", Patent No. 0008440, France, 29/06/00.

Sule-Suso, J, Forster, A, Zholobenko, V, Stone, N, El Haj, A., "Effects of $CaCl_2$ and $MgCl_2$ on Fourier transform infrared (FT-IR) spectra of lung cancer cells", *Appl. Spectrosc.*, 2003.

Cricenti, R. Generosi, M. Luce, P. Perfetti, G. Margaritondo, D. Tayley, J.S. Sanghera, I.D.Aggarwal, N.H.Tolk, A. Congiu Castellano, M. Rizzo and Piston, "Chemically resolved imaging of biological cells and thin films by infrared scanning near-field optical spectroscopy", *Biophys. J.*, **85**, 2705-2710, 2003.

Lasch P., Haensch W., Kidder, L., Lewis, E.N. and Naumann D., "Colorectal adenocarcinoma characterization by spatially resolved FT-IR microspectroscopy", *Appl. Spectrosc*. **56**, 1-9, 2002.

A.M. Melin, A. Perromat, C. Lorin, G. Deleris, "Gamma-irradiation and cellular damage in Kocuria rosea: investigation by one- and two-dimensional infrared spectroscopy", *Arch. Biochem. Biophys.*, **408**, 211-219, 2002.

PARTICIPANT 4 – BIOLOGISTS
Team Coordinator: Marco Colombatti (Verona, Italy)

Node 4 is formed by several laboratories dealing with biological applications of infrared spectroscopy. The role of this node will be to set up and select appropriate cell culture models and tissues to study fundament aspects of cell physiology and of modifications associated with specific pathologic processes. To this end stimulations and treatments affecting discrete biochemical pathways of normal and pathologic cells will also be carried out. Specimens and models prepared and manipulated by researchers of node 4 will be exchanged among other participating nodes for analysis by infrared spectroscopy.

Name	Position	Affiliation	Relevant expertise
Marco Colombatti	Associate Professor of Immunology	Medical School, University of Verona, Italy	Experimental models of tumor immunoterapy; Mechanisms of cell intoxication by toxins; development of macromolecular anti-tumor reagents
Giuseppe Bellisola	Senior researcher	Medical School, University of Verona, Italy	Oxidoreductive reactions, analysis of human tissues and samples (INAA, PIXE, XRF)
Marek Lankosz	Professor of Medical Physics	Faculty of Physics and Nuclear Techniques, AGH-University of Science and Technology, Krakow, Poland	Analysis of human tissue samples and living cells in culture using synchrotron XRF, XANES and IR
Szczerbowska-Boruchowska	Medical physicist	Faculty of Physics and Nuclear Techniques, AGH, University of Mining and Metallurgy, Krakow, Poland.	Analysis of organic and inorganic compounds in human central nervous system tissue, IR microspectroscopy, synchrotron microbeam x-ray fluorescence.
Gianfranco Menestrina	Director of the Section	CNR Institute of Biophysics, at Trento, Italy	Mode of action of bacterial, animal and plant toxins on cells and model membranes; Structural characterisation by FTIR spectroscopy; Immunotoxins.
Mauro Dalla Serra	Researcher	CNR Institute of Biophysics, at Trento, Italy	Spectroscopy techniques, computer resources, statistical data analysis, bioinformatics
Rainer Pepperkok	Research Team Leader	Cell Biology and Cell Biophysics Programme, EMBL Heidelberg, Germany	Membrane traffic in the early secretory pathways, light microscopy and fluorescence microscopy of living cells
Michael Keese	Researcher	Cell Biology and Cell Biophysics Programme, EMBL Heidelberg, Germany	Clinical medicine, cell biology
Nick Stone	Senior Clinical Scientist	Gloucester Royal Hospital, Cheltenham, U.K.	Analysis of precancer and cancer tissue to determine characteristics, particular reference to Barrett's oesophagus

Fariba Bahrami	Research Scientist	SRS synchrotron facility, Daresbury, U.K.	Collagen degradation as a biomarker for cancer; Application of SR techniques in Environmental samples
Fiona Lyng	Research Scientist	Dublin Institute of Technology, Ireland	Application of IR and Raman spectroscopy to the diagnosis of cervical cancer and pre-cancer
Eoghan Ó Faoláin	Researcher	Dublin Institute of Technology, Ireland	Application of vibrational spectroscopy to the diagnosis of cervical cancer and pre-cancer

Recent relevant publications:

G. Fracasso, G. Bellisola, S. Cingarlini, S. Righetti, E. Chiesa, D. Castelletti, T. Prayer-Galetti, F. Pagano, G. Tridente, and M. Colombatti, "Anti-tumor effects of toxins targeted to the prostate specific membrane antigen", *Prostate*, **53**, 9-23, 2002

M. Szczrbowska-Boruchowska, M. Lankosz, J. Ostachowicz, D. Adamek, A. Krygowska-Wajs, B. Tomik, A. Simionovici and S. Bohic, "Application of Synchrotron radiation for elemental microanalysis of human central nervous system tissue", *J. Phys. IV France*, **104**, 325-328, 2003

Anderluh, G., M. Dalla Serra, G. Viero, G. Guella, P. Macek, and G. Menestrina, "Pore formation by equinatoxin II, an eukaryotic protein toxin, occurs by induction of non-lamellar lipid structures", *J. Biol. Chem.* **278**, in press

J. Anastassopoulou and T. Theophanides, "Magnesium-DNA interactions and the possible relation of magnesium to carcinogenesis. Irradiation and free radicals" *Oncology and Haematology*, **42**, 79-91, 2002

Stephens DJ, Pepperkok R., "Imaging of procollagen transport reveals COPI-dependent cargo sorting during ER-to-Golgi transport in mammalian cells", J Cell Sci. 2002 Mar 15;115(Pt6):1149-60.

PARTICIPANT 5 – CLINICIANS
Team Coordinator: Sheila Fisher (Leeds, UK)

Supporting and increasing clinician involvement is a key objective of the SSA bid. This node comprises committed clinicians in established and emerging research partnerships which use infrared microspectroscopy. This common technology is applied to a range of conditions including cancer (encompassing various sites and aspects from cytology, characterisation of tumours, analysis of the invasive front and detection of metastatic disease), bacterial and possibly viral characterisation and the assessment of other important diseases such as cardiovascular and neurological conditions. In some areas, notably cancer, evolving and established partnerships exist with basic scientists and links to synchrotrons are, or are becoming established. Yet in many important areas, scientists are working alone without partners to provide a clinical perspective. The lack of pan-European coordination leaves some countries particularly strong in this regard and there is a need to encourage greater clinician input in those countries where it is lacking. Through the SSA, we aim to widen clinical partnership in research and the range of diseases for which collaborative groups are functional.

Name	Position	Affiliation	Relevant expertise
Sheila E. Fisher	Senior Lecturer/Hon Consultant in Maxillofacial Surgery	University of Leeds, U.K.	Oral cancer, FT-IR Characterisation of cancer & precancer
Ken A. MacLennan	Professor of Tumour Pathology	University of Leeds, U.K.	Staging and prognostic features of tumour biology
Hugh Barr	Professor of Surgery	Gloucester Royal Hospital, Cheltenham, U.K.	Application of spectroscopy to clinical tumour assessment; Use of different modalities of spectroscopy
Colin Hopper	Head of Oral and Maxillofacial Surgery	University College Hospital, London, U.K.	Use of spectroscopy in cancer detection and photobiology
Noel Clarke	Consultant Surgeon	Christie Hospital, Manchester, U.K.	Urological tumours (including prostatic)
Peter Gardner	Senior Lecturer	University of Manchester Institute of Science and Technology, U.K.	Use of infrared microspectroscopy to detect bony metastatic disease
Ian Symonds	Senior Lecturer in Obstetrics and Gynaecology	University of Nottingham, U.K.	Infrared microspectroscopy in the analysis of cervical smears for precancer and cancer diagnosis
Josep Sulé-Suso	Associate Specialist in Clinical Oncology	Staffordshire Oncology Centre, North Staffordshire Hospital Trust, U.K.	Infrared microspectrocopy, diagnosis of lung cancer, tumour immunology, effects of chemotherapy and radiotherapy on cancer cells
Mary Hunter	Medical Scientist	National Maternity Hospital, Dublin, Ireland	Application of vibrational spectroscopy to the diagnosis of cervical cancer and precancer
Michel Pluot	Professor of Anatomo-Pathology	Robert Debré Hospital, Reims, France	Histopathology and cytology, neurology, diagnostic of thyroid and brain tumours
Val Clerehugh	Deputy Director of Research,	Leeds Dental Institute, University of Leeds, UK	Investigation of microflora in aggressive periodontal disease in diabetic patients
Colin Robinson	Professor of Oral Biology	University of Leeds, UK	Biofilm technology and characterisation of bacteria by spectroscopy, including photobiology
Dominique Toubas	Mycologist	Maison Blanche Hospital, Reims, France	Physiopathology of candidiasis, candida-epithelial cell interaction
Jörg Storm	Chief Surgeon	Surgical Clinic of the University Clinic Mannheim, Germany	Tumour surgery, especially liver and pancreas
Sylvain Rubin	Surgeon	Cardio-vascular and Thoracic Surgery Dept., Robert Debré Hospital, Reims, France	FTIR/Raman microscopy of human aortic samples, predictive and diagnostic markers of aneurysms
Christine Clavelle	Professor of Cellular Biology	Pol Boin Laboratory, Reims University Hospital, France	HPV-cell interaction

Recent relevant publications:

M. J. Tobin, F. Rutten, M. Chesters, J. Chalmers, I. Symonds, S. Fisher, R. Allibone, A. Hitchcock, "Investigating the potential for infrared microanalysis in cancer screening", *Eu: Clin. Lab.* **21**, 20-22, 2002

M. Patey, B. Delemer, G. Bellon, L. Martiny, M. Pluot, B. Haye., "Immunohistochemical study of thrombospondin and its receptors in normal thyroid and in thyroid tumours", J. Clin. Path., **52**, 895-900, 1999..

Rubin S, Baehrel B. “When to pose a surgical indication for type III aortic dissection?”, MD thesis, Faculty of Medicine, University of Reims, 2001

C. Sandt, G.D. Sockalingum, D. Aubert, H. Lepan, C. Lepouse, M. Jaussaud, A. Leon, J.M. Pinon, M. Manfait, D. Toubas. “Use of Fourier-transform infrared spectroscopy for typing of Candida albicans strains isolated in intensive care units”. *J Clin. Microbiol*. **41**, 954-9, 2003

Clavel C., “Value of cervical screening by HPV DNA testing. It is legitimate to type HPV for the primary screening of cervix neoplasms”, *Gynecol. Obstet. Fertil.* **30**,:896-8, 2002

NON-EUROPEAN ASSOCIATES

The following non-European researchers have expressed their strong interest in the DASIM proposal and their desire to participate in the activities described in the DASIM proposal at the level allowed under FP6 rules. All are internationally recognized experts of the highest possible standing in the field applications of infrared microspectroscopy to tissue/cell characterization and diagnostics.

Max Diem, City University of New York, U.S.A.
Hoi-Ying Holman, Lawrence Berkeley Laboratory, U.S.A.
Lisa Miller, Brookhaven National Laboratory, U.S.A.

A strong interest and the desire to participate in the DASIM proposal has also been expressed by Prof. Wu Ziyu, the Research Director of the Beijing Synchrotron Radiation Facility of the IHEP. Prof. Tang Jin Tian, Clinician and Director of the China-Japan Friendship Institute of Clinical Medical Sciences, is strongly interested in a collaboration with the Beijing Synchrotron Radiation Facility in this field.

SSA Project Effort Form
Full duration of project
(insert person-months for activities in which partners are involved)

Project acronym -

	COORDINATOR	SYNCHROTRONS	SPECTROCSOPISTS	BIOLOGISTS	CLINICIANS	TOTAL PARTNERS
Support activities						
WP1 Meeting 1	0.5	3	2	2	2	9.5
WP2 Meeting 2	0.5	3	2	2	2	9.5
WP3 Meeting 3	0.5	3	2	2	2	9.5
WP4 School	2	4	4	4	3	17
WP5 Meeting 4	0.5	4	4	4	4	16.5
WP6 Virtual Knowledge Park	3	15	15	15	25	73
WP7 Web Site	1	1	1	1	1	5
WP8 Book	2	5	3	3	3	16
WP9 Workgroups (50%)	0.75	10	10	10	10	40.75
WP10 Final Report	1	1	1	1	1	5
Total management	**11.75**	**49**	**44**	**44**	**43**	**201.75**
Management activities						
WP9 Workgroups (50%)	0.75	10	10	10	10	40.75
Total support activities	**0.75**	**10**	**10**	**10**	**10**	**40.75**
TOTAL ACTIVITIES	**12.5**					

B.5 Project management

The DASIM consortium came into being at the "1st Workshop on Biological Applications of Synchrotron Infrared in Europe", in Karlsruhe, Germany on 11-12 September 2003. Discussions were held amongst the participants on the possibility of the submission of a FP6 proposal, during which research topic LSH-2003-1.2.2-4: "Advances in synchrotron radiation techniques for diagnostic purposes" was identified as directly relevant to the work of some of the workshop participants.

Following the workshop, the discussions continued via e-mail. Suggestions for the role of coordinator and for membership of an Executive Board were circulated and discussed, resulting in the appointment of a Board consisting of David Moss (Karlsruhe) as coordinator, Augusto Marcelli (Frascati), Sheila Fisher (Leeds), Peter Lasch (Berlin), Ganesh Sockalingum (Reims), Marco Colombatti (Verona) and Mark Tobin (Daresbury). This Executive Board has prepared the present proposal for submission, and will continue to take overall managerial responsibility until the Launch Meeting in month 0.

From month 0, the topmost authority for decision-making will be the general assembly of all participants. This will meet annually at the Annual Meetings and will make its decisions by simple majority voting of those attending. The first general assembly will decide on composition and membership of the Executive Board.

The Executive Board will take overall managerial, administrative and financial responsibility for implementing the program set out in Section B.4 in accordance with the decisions of the general assembly. It will meet twice yearly, once at the Annual Meetings and once in between. It will have the right to invite any person from inside or outside the consortium to attend its meetings as non-voting guests, if their presence is need for the business at hand.

The lower tier of management are the Workgroups. These will take responsibility for a particular defined aspect of the consortium's work program. We envisage cross-disciplinary Workgroups to manage specific aspects of the consortium's coordinating and structuring functions (examples: Cancer Diagnosis Workgroup, Data Processing Workgroup); WP Workgroups to manage a specific Work Package (examples: Organizing/Program Committee for an Annual Meeting, VKP Workgroup); and single discipline Workgroups to manage the dissemination of consensus information and expertise to other participants (examples: Clinicans Workgroup, Beamline Scientists Workgroup). We also envisage Research Consortium Workgroups, consisting of scientists and clinicians who have made contact via the DASIM Meetings and/or VKP and who wish to plan specific collaborative research. The latter will need meetings to plan research, carry out pilot experiments and formulate joint research proposals.

The management activities of the Workgroups are covered by Work Package 9. Funding required for these management activities includes travel and hotel expenses to enable Workgroup members to attend Workgroup meetings. Where possible, Workgroup meetings should take place during the Annual Meetings so that no additional expense is occurred, and the program for the Annual Meetings will provide "parallel session time" to facilitate this. Workgroups will also be expected to minimize the number of face-to-face meetings required by making full use of electronic communications for the conduction of their business, in particular via the VKP. All of these provisions apply equally to the Executive Board.

Intellectual property rights:

Since an SSA does not provide research funding, the DASIM consortium makes no claim to intellectual property rights arising through the research work of its participants. Participation in the DASIM network incurs no obligation to release confidential information to any other person, whether within or outside the consortium. The work of the DASIM consortium with respect to research data, experimental methods, written materials and inventions consists only of evaluating, comparing and disseminating such materials as are already published, released for publication or otherwise in the public domain. Each participant or group of participants takes responsibility for management of intellectual property rights arising from their own work.

B.6 Workplan

The stated aim of DASIM is to coordinate, manage and disseminate the international research effort in the characterisation and classification of biological tissues and cells using synchrotron infrared spectroscopy, in order to accelerate the application of this science for practical clinical diagnosis and to promote acceptance of the technique amongst the medical and health communities.

This is an ambitious but important multidisciplinary project with key objectives in the areas of research, education and project management. It comprises a range of support and managerial activities.

Support activities:

The support activities are defined as those which directly contribute to the scientific aims of the project. These can be divided into scientific, educational and project management activities.

Scientific objectives:

- Coordination and facilitation of existing and emerging research groups
- Widening participation to those who do not currently have access to synchrotron facilities
- Widening the application of synchrotron based infrared microspectroscopy across the diagnostic spectrum
- Exploration of the key areas in clinical diagnosis to which infrared spectroscopy can make a major contribution
- Exploration of technical issues relating to infrared microspectroscopy required to best support clinical applications
- Exploration of complementary technology which may be used in conjunction with infrared microspectroscopy
- Opportunities for translational research
- Recommendations for a sustained programme of fundamental, clinically relevant research at the international level to develop the technology to its full potential

Educational objectives:

- Informing the medical and wider health care community of the potential of infrared microspectroscopy in clinical medicine
- Providing a current and reliable source of data regarding progress in this area
- Providing access and training opportunities for current and future clinical and scientific researchers
- Organize an international school of infrared microspectroscopy to train young scientists

Project management:

- Formation and maintenance of an effective and coherent management structure to oversee the project
- Formation of working and expert groups to progress the scientific objectives
- Use of appropriate technology to ensure that the project can be conducted in the most efficient and effective way

- Use of meetings to add coherence to the groups, allow face to face presentation and evaluation of existing and new projects to avoid duplication of effort and to forge links between multidisciplinary teams
- Use of the school to form new young researchers from all areas involved in the project
- Preparation of reports
- Preparation of a book to inform current and prospective researchers from a multidisciplinary background

The above relate to support activities to allow the project to reach a successful outcome.

Managerial activities:

These are defined as the activities which allow the project to be organised but which do not directly relate to its scientific or educational outcomes

Managerial activities:

- Financial support
- Secretarial support
- Consumables

Summary:

Although these are far reaching, these activities come together to form a coherent programme making the most effective use of the multidisciplinary nature of the SSA.

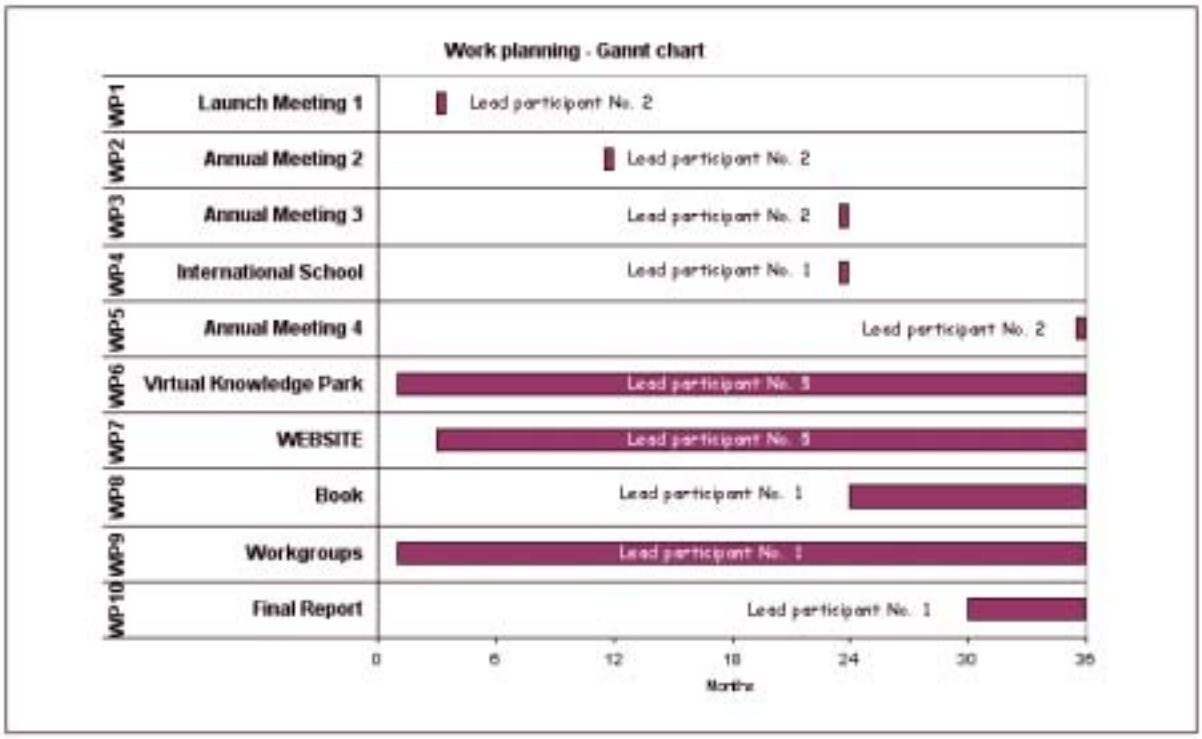
Overview of structure of project:

The overall structure is to set key points at which major meetings will take place and overall progress reviewed and documented. These are each linked to key outputs, either a report or, by the end of the project, a book, which will form a readily verifiable record of the achievements of the group. To maintain contact and progress, the innovative development of the Virtual Knowledge Park [VKP] will be used to offer support to the group as a whole and to individual working and expert groups within the overall framework of the project. It can also act as a resource for all members of the multidisciplinary team to inform and update on areas outside the individual's own specialist field. In this way it can support established members and give a focussed overview to new scientists, clinicians and members of the planned international school.

The most important factor in success is the choice of participants. All have a defined place in the programme of activities. Synchrotron scientists have access to complementary technology at the forefront of European expertise. The biological spectroscopists and biologists offer complementary understanding and expertise in the nature of spectral interpretation in biological systems and in the biological behaviour of tissues. The clinicians have complementary interests associated with the clinical needs and the potential for a translational element to the research, covering the range of issues identified under 'scientific objectives'. All participants have been active in research and in the training and development of future researchers. The lead in the VKP initiative [SEF] is a course leader and an experienced clinical teacher at Postgraduate level, an examiner at national level and has higher training and current grant funded involvement in innovative educational techniques in surgery.

As part of our preparation for this bid, members of the group have hosted successful multidisciplinary conferences, in the UK and Germany respectively. The executive team was appointed as a result of open discussion at those meetings and enjoys the confidence and support of all participants. Therefore, the preparatory work to this proposal has been completed thoroughly and successfully and gives a foundation for the continuation of similar networking as part of this proposal. The SSA gives a much more defined focus and coordination than we have been able to achieve unaided but the attributes to achieve success have already been tested.

b) Work planning, showing the timing of the different WPs and their components

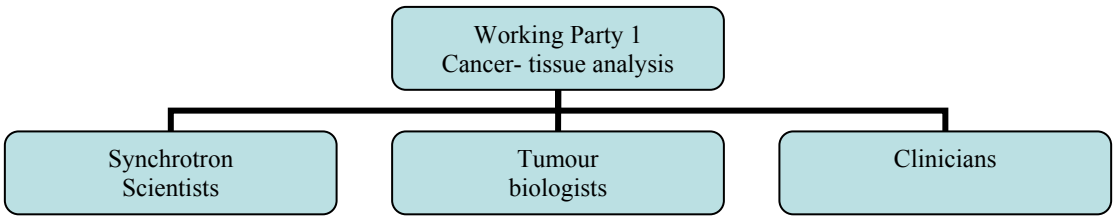


b1) Overall project plan and monitoring:

Planning phase (first 3 months)
Executive meeting
Setting up VKP
Listing of introductions and expertise by defined proforma

↓

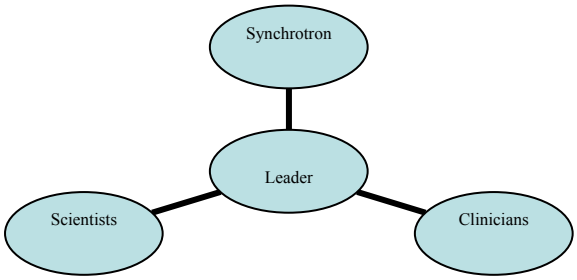
'Launch' meeting (3 months)
Presentation of plans for project
Discussion
Introduction to the VKP
Setting up of working parties (WPs): each with a multidisciplinary structure, as below, to address the scientific and educational issues



Whilst multidisciplinary membership will be expected in all groups, some will have enhanced participation by specific groups, for example, *'exploration of technical issues relating to infrared microspectroscopy to best support clinical applications'* will have a relatively wide synchrotron scientist involvement, whereas *'exploration of the key areas in clinical diagnosis'* will involve a spectrum of clinicians.
Each working party will elect a Leader to oversee agreed actions

↓

Working groups



Coordination and contact will take place using the VKP for document management, electronic messaging and video conferencing to ensure that groups maintain contact
The Leader will have responsibility for allocating tasks and for reporting back on a quarterly basis to the Executive.

↓

Reporting
Short report to the Executive
Posted report in the general project area of the VKP

This cycle will repeat quarterly for year 1.

↓

Meeting, Year 1: Evaluation of progress
Executive report
Working group reports
Scientific presentations
Discussion: project progress- areas to be continued/expanded/abandoned
- areas that may merit a further application
- dissemination/publications
-need to involve new/changed expertise
Working plan for Year 2
Setting up application for short term 'taster' scholarships in lead areas (2)

↓

Working groups
Continue evolution of projects
Define strategy for dissemination/development/publication
Posting of progress
Where available and IPR protected, where necessary, transfer of summary to open area
Networking/conferencing via VKP
Quarterly reports to Executive

↓

Meeting, year 2
Reports and redefine strategies as for year 1
Emphasis on results and implications for clinical diagnosis
Emphasis on projects to develop further
Planning of book, chapters/authors
Planning of the international school, invited lectures, etc.
Workshop reviews, reorganisation where needed

↓

Working groups
Work to complete, write up and disseminate results
Commence preparation of 'follow on' initiatives
Network with other groups to maximise potential and interdisciplinary coordination of follow on projects
Reports to Executive and to open site

↓

Executive meeting (30 months)
Receive drafts of chapters
Receive reports
Set strategy for future actions
Prepare for major open scientific meeting

↓

Scientifically led multidisciplinary meeting
Evaluation and Closure
Submission of 'follow on' studies

Notes: the multidisciplinary nature of the SSA and the requirement to define and evaluate key areas within a 3 year timescale means that a number of workgroups (WG) will operate for the duration of the project. It is expected that, as initiatives develop or prove unsustainable the focus, membership and size may change. All WGs will be directly linked to the Executive who will reserve the right to intervene in the light of unsatisfactory progress and to withdraw funding from any initiative that is failing to demonstrate progress according to its documented objectives.

We expect approximately 5 WGs to be operational at any given period, the emphasis changing from exploration of potential to defined future projects as the SSA progresses.

The WGs also have lowest-tier management responsibilities for their individual aspects of the program. Further details and examples of WGs are given in Section B.5

b2) Workpackages

WP1- Launch meeting
Deliverables: Project plan on VKP Project Area (Executive)
Membership of Working groups, remit and plans (Leaders)
Abstracts of scientific presentations [site and 'book' form]

WP2- First Annual Meeting
Deliverables: Progress report and updated project plan on VKP (Executive)
Update on working groups, results and plans (Leaders)
Abstracts of scientific presentations [site and 'book' form]

WP3- Second Annual Meeting
Deliverables: Progress report and updated project plan on VKP (Executive)
Update on working groups, results and plans to complete/?future Initiatives
Abstracts of scientific presentations
Report of experience by recipients of 'taster' scholarships

WP4- International School
Deliverables: Lectures book

WP5- Final meeting
Deliverables: Final report (Executive)
Summary of planned further initiatives
Evaluation of success of project
Abstracts of scientific presentations (it is expected that this will be an open meeting and represent a 'showcase' of the project to a wider audience).
Publication of abstracts and keynote papers in book form as 'Proceedings'.

WP6- Virtual Knowledge Park
This is a new HEFCE-funded initiative available to approved higher education users at a much lower than commercial cost.
Background Information: The Virtual Knowledge Park (VKP) software originally began development within the University of Leeds in 1996 and has been supported by an investment of almost £2M over the last 7 years. Part of this investment was supported by the Higher Education Funding Council for England (HEFCE), who awarded the University of Leeds £267k from the Good Management Practice Fund to develop the collaborative tools. This represented the highest single award for 2000. Due to the success of the project, follow-on funding of £145k has since been awarded for dissemination of the system within the Higher Education sector.

Services relevant to the requirements of the project include:
Document Management, Review and Publication Protocols: The VKP provides a comprehensive range of tools including document management, discussion groups and video conferencing, which enable geographically dispersed team members to share information, discuss project issues and jointly modify team resources, if necessary in real time. The available document management facilities allow for any electronic file to be made available to the wider community in any format. Strict access control mechanisms and version control provides support for managed peer review processes.
Access to Knowledge Collections: The VKP can be used as a central storage mechanism for all activities associated with a project. As a result knowledge collections will automatically

be generated, these can be made up of discussion threads, documents, e-mail and academic expertise, all of which are fully searchable through full text searches of content.
Web-Based Resources for Knowledge Sharing: A fully flexible suite of discussion boards is available, encouraging team members to share both explicit and tacit knowledge. This applies very much to the multidisciplinary aspect of the SSA allowing members to access material and to post questions on the discussion board about specialist areas other than their own.
Interoperability with Other Web Based Resources and Databases: Direct access can be provided to resources held in the VKP from all web based systems.
Information Dissemination and Public Access : The VKP incorporates a flexible security model which supports both open access to public information and strictly controlled access through security permissions. It is therefore possible to provide quick and easy public access, either through the VKP or through VKP resource URLs that are embedded within other web interfaces, such as web pages. For the SSA the best strategy is to use the VKP to compile material and then post it onto a designated web-site linked to specialist and disease orientated health websites.
Video-Conferencing: Point-to-point and multi-way videoconferencing is available for PC users and can support up to 10 people simultaneously. This utilises the free software of Net Meeting or Meeting Point. The potential is to set up meetings where any issue arises requiring discussion rather than a longer meeting adding flexibility to manage the SSA in an interactive way. It can also be used to link multinational groups for a focussed discussion on a specific research question. However, because of the scope of the project it is seen as additional to major review meetings as these are likely to be complex and lengthy and to benefit from face to face contact.

WP7- Website
Although the VKP will be central to the project management and can be accessed by the public one key aim is to gain understanding and acceptance of the technology in the wider medical, health and scientific communities.
We will use selected material to illustrate the main focus of our work and important and developing areas and link that to selected websites in the target areas. For many this will be a simple way to explore the work. For those with a greater interest invitation links to 'subscribe' to VKP discussion areas will be offered, within the VKP's capacity of 250 active users.

WP8- Book
As a lasting means of education and dissemination of its results to the scientific and medical communities, the DASIM consortium will publish a multi-author volume on diagnostic applications of synchrotron infrared microscopy. Each chapter will cover one area of the field and will be authored by experts in this area. The individual contributions will be written in language comprehensible to all participants in this field from physicists to clinicians.

WP9- Workgroups
This work package covers the Workgroup operations as detailed above and in Section B.5, (including the operations of the Executive Committee).

WP10- Final Report
The final scientific meeting will form a 'showcase' for the achievements of the SSA. It will be opened to all interested parties at as low a cost as can be achieved and will represent the

transition between the SSA and the focussed follow on projects which we believe and hope will arise from the effective working and networking the SSA has allowed.
Together with this, we will draw together a multidisciplinary assessment of Synchrotron Infrared Microspectroscopy and the main research findings in the book [WP7] and prepare the final submission according to the requirements of the European Commission.

b3) Risk management strategy
The following risks have been considered and are presented together with contingency plans.

Specific risks and strategies:
1. Technical problems with synchrotrons. The inclusion of a network of synchrotrons and of the wider international community allows contingency plans to carry out time sensitive work on a partner facilities.
2. Refusal of beam time applications: key members of each synchrotron management team are involved in the project, which will facilitate passage of beamtime applications through each facility's peer review procedures. In case of problems, as with point 1 the breadth of the network will permit strategic shifting of time-sensitive work to facilities where beamtime is available.
3. Inability to support the project by lack of key expertise. The Nodes have been established by attention to the skills required to bring this SSA project to a successful conclusion. It is expected that contingencies will arise where expenditure may be needed for a specific skill (e.g. in analysis of material which is important for project evaluation). A sum has been included in the overall budget to cover such eventualities and all steps have been taken in the composition of the groups to avoid foreseeable deficiencies in expertise.
4. Loss of a key group member/team. The size of the project and the plans for interdisciplinary working are such that the project will never be dependent solely on a given individual or small group.
5. Lack of progress in that the potential of synchrotron infrared microspectroscopy falls demonstrably short of expectations derived from studies to date. The Executive group have an ongoing remit to monitor progress. If necessary, negotiations would be held with the Commission for the early closure of the project.
6. IT risks: the integrated technology of the VKP will enhance the project. Should this fail, the project will default back to standard web-based dissemination and electronic communication. Such an event would cause difficulties with the kind of sophisticated interaction required for such a major project, especially with regard to the provision of secure environments, document management etc. but these could be overcome by the use of alternative strategies.

c) Graphical presentation of the components showing their interdependencies

Project Resources

This section deals with the calculation and distribution of the project's financial resources, and explains the calculation of the figures given in Section A.3.

WP1 – WP3 and WP5
Four Annual Meetings, each to be held at a different synchrotron facility, therefore Lead Participant is Participant 2.

Cost calculation:

Assumptions:
All active DASIM participants will have their full costs met.
80% of active members will attend
Cost of travel, hotel x 2 nights, subsistence and venue approx. ; 750 Euros per person
We will want two international speakers per conference @ 2,500 Euros each
We would like to award 5 student or young researcher bursaries @ 750 Euros each.

Without and admin costs that comes to: approx 43 active participants, assume 34 will attend.
Active members, 34 @ 750 Euros = 25,500
Guest speakers 2@ 2,500 Euros = 5,000
Bursaries for students and young researchers 5 @ 750 Euros = 3,750

TOTAL = **34,250** per WP
With indirect costs = **39,388** per WP

WP4
International School, to be held at a synchrotron facility - probably ANKA, Forschungszentrum Karlsruhe, Germany, though this is to be confirmed. Lead participant is Participant 1, as currently the most likely host.

Cost calculation:
Format, scope and scale will be similar to Annual Meetings, therefore **€ 34250** as for WP1-WP3 and WP5, with indirect costs **€ 50552**.

WP6
Virtual Knowledge Park, lead participant is Participant 5.

Cost calculation:
Establishing building, rooms, hierarchical access for three year 'tenancy'
£29,475= 42,650 Euros (+VAT@17.5%, if applicable) = **50,114**
Operational costs: access, updates etc. £10,000 pa x 3= 43,410+VAT=**51,007**
IT support and staffing based on Clerical Grade 4 [PA level]. Assuming 3.5% annual increase in salary and NI and pension paid= £62,463=**90,384** Euros
Overheads on staffing @20%= **18,077**
Total costs of VKP to support project for 3 years= **191,505**
Note: The post included in this section will allow support at secretarial and document management level for the project as a whole and allow economies of scale in secretarial support overall.
20% overhead (AC model) = 229,806

WP7
Website, lead participant is Participant 5. Whilst the VKP will support the networking, planning, workgroup and document handling functions, we also need a website for wider access and to link to medical and ?patient related websites for the future.

Cost calculation:
For domain registration, web hosting and professional design services: **10,000**
20% overhead (AC model) = 12,000

WP8
Book, lead particpant is Participant 1 because Coordinator will be editor of book.

Cost calculation:
For 700 pages, 12-15 chapters, colour illustrations throughout, hard covers: Informal, non-binding estimate provided by Springer Verlag: 5**0,000,** with indirect costs **€ 66302**

WP9
Workgroups. Lead participant is Participant 1, to administer a general travel fund

Cost calculation:
Assumptions:
Each senior (i.e. named section B.4) will be involved in one workgroup on average, attending one meeting of his WG per year (other than WG meetings during the Annual Meeting).
Average cost of European travel, hotel x 1 night, subsistence approx. 500 Euros per person

43 x 500 = **21,500 per year = 64,500 total,** with indirect costs **€ 92056 (€ 44476** for Support, **€ 47580** for Management)

Due to dual purpose of Workgroups (Support/Management), this indirect sum split 50:50 between Support and Management activities.

WP10
Final Report, lead participant is Participant 1.

No direct costs anticipated that are not already covered in **WP6** and **WP9**.

With indirect costs **€ 8151**

d) Detailed work description broken down into workpackages:

Workpackage list (full duration of project)

Work-package No[1]	Workpackage title	Lead participant No[2]	Person-months[3]	Start month[4]	End month[5]	Deliv-erable No[6]
WP1	Launch Meeting (1)	2	9.5	3	3	1
WP2	Annual Meeting (2)	2	9.5	12	12	2
WP3	Annual Meeting (3)	2	9.5	24	24	3
WP4	International School	1	17	24	24	4
WP5	Annual Meeting (4)	2	16.5	36	36	5
WP6	Virtual Knowledge Park	5	73	1	36	6
WP7	Website	5	5	3	36	7
WP8	Book	1	16	24	36	8
WP9	Workgroups	1	40.75	1	36	
WP10	Final Report	1	5	30	36	9
	TOTAL		201.75			

[1] Workpackage number: WP 1 – WP n.
[2] Number of the contractor leading the work in this workpackage.
[3] The total number of person-months allocated to each workpackage.
[4] Relative start date for the work in the specific workpackages, month 0 marking the start of the project, and all other start dates being relative to this start date.
[5] Relative end date, month 0 marking the start of the project, and all ends dates being relative to this start date.
[6] Deliverable number: Number for the deliverable(s)/result(s) mentioned in the workpackage: D1 - Dn.

Deliverables list (full duration of project)

Deliverable No[7]	Deliverable title	Delivery date [8]	Nature [9]	Dissemination level [10]
D1	Abstracts Book, Meeting 1	0	R	PU
D2	Abstracts Book, Meeting 2	12	R	PU
D3	Abstracts Book, Meeting 3	24	R	PU
D4	Lectures Book, International School	24	R	PU
D5	Abstracts Book, Meeting 4	36	R	PU
D6	Virtual Knowledge Park	3	O	PP
D7	Website	6	R	PU
D8	Book	36	R	PU
D9	Final Report	36	R	PU

[7] Deliverable numbers in order of delivery dates: D1 – Dn.
[8] Month in which the deliverables will be available. Month 0 marking the start of the project, and all delivery dates being relative to this start date.
[9] Please indicate the nature of the deliverable using one of the following codes:
R = Report
P = Prototype
D = Demonstrator
O = Other
[10] Please indicate the dissemination level using one of the following codes:
PU = Public
PP = Restricted to other programme participants (including the Commission Services)
RE = Restricted to a group specified by the consortium (including the Commission Services)
CO = Confidential, only for members of the consortium (including the Commission Services)

Workpackage description (full duration of project)

Workpackage number	WP1	**Start date or starting event:**				Month 0
Participant id		2	3	4	5	1
Person-months per participant		3	2	2	2	0.5

Objectives

Annual Meeting 1: Launch Meeting

Description of work

Planning of project (template prepared by Executive)

Consideration of groups to share expertise

Multidiscipinary exchange of scientific material by presented papers

Formation of working parties- small group discussions

Deliverables

D1 – Abstracts book of the 1st Annual Meeting

Milestones[11] and expected result

Working groups formed.

Posting of membership and work plans, responsibilities and timescale on VKP

Short summary for webpage

[11] Milestones are control points at which decisions are needed; for example concerning which of several technologies will be adopted as the basis for the next phase of the project.

Workpackage description (full duration of project)

Workpackage number	WP2	**Start date or starting event:**				Month 12
Participant id	2	3	4	5	1	
Person-months per participant	3	2	2	2	0.5	

Objectives

Annual Meeting 2: First Mid-Term Meeting

Description of work

Review of progress

Presentations by each work group and free papers to facilitate evolution of projects

Free scientific papers

Discussion and agreement re next phase

Continuation or changes to working groups as necessary for next phase

Deliverables

D2 – Abstracts book of the 2nd Annual Meeting

Milestones[12] and expected result

Progress report (overall) on VKP

Refocus on most promising areas confirmed

New partners participants integrated into focussed research network

[12] Milestones are control points at which decisions are needed; for example concerning which of several technologies will be adopted as the basis for the next phase of the project.

Workpackage description (full duration of project)

Workpackage number	WP3	**Start date or starting event:**				Month 24
Participant id		2	3	4	5	1
Person-months per participant		3	2	2	2	0.5

Objectives

Annual Meeting 3: Second Mid-Term Meeting

Description of work

As for first midterm meeting but starting to focus on results and promising areas for expansion and/or follow on projects

Deliverables

D3 – Abstracts book of the 3rd Annual Meeting

Milestones[13] and expected result

As for earlier first mid term meeting

[13] Milestones are control points at which decisions are needed; for example concerning which of several technologies will be adopted as the basis for the next phase of the project.

Workpackage description (full duration of project)

Workpackage number	WP4	**Start date or starting event:**				Month 36
Participant id		1	2	3	4	5
Person-months per participant		2	4	4	4	3

Objectives

International IR microspectroscopy School

Description of work

Multidisciplinary event to teach multidisciplinary aspects of synchrotron spectroscopy to young scientists/clinician scientists and those experienced researchers who are integrating synchrotron infrared microspectroscopy research into their own fields

Deliverables

D4 – Lectures book of the International School

Milestones[14] and expected result

Increasing the expertise, not only within the group but to the wider scientific and clinical communities.

A measure of our success in collaborating research and widening access and understanding of its potential will be the level of interest and participation in this school

[14] Milestones are control points at which decisions are needed; for example concerning which of several technologies will be adopted as the basis for the next phase of the project.

Workpackage description (full duration of project)

Workpackage number	WP5	**Start date or starting event:**				Month 36
Participant id	2	3	4	5	1	
Person-months per participant	4	4	4	4	0.5	

Objectives

Annual Meeting 4: Concluding Meeting

Description of work

A 'showcase' of the achievements of the project

Keynote, summary and free papers, open to members as part of the project, to others by registration and payment of a 'cost basis only' fee.

Final summaries by Working Group leaders

Decisions as to future projects- whole or small group format

Deliverables

D5 – Abstracts book of the 4th Annual Meeting

Milestones[15] and expected result

Affirmation and dissemination of the results collaborated through the SSA

Continuing active Pan European Research Partnerships

[15] Milestones are control points at which decisions are needed; for example concerning which of several technologies will be adopted as the basis for the next phase of the project.

Workpackage description (full duration of project)

Workpackage number	WP6	**Start date or starting event:**			
Participant id	5	2	3	4	1
Person-months per participant	25	15	15	15	3

Objectives

Virtual Knowledge Park

Description of work

The central resource for collection, management and dissemination of work ongoing as part of the project

The virtual 'home' of the Executive Management Team and the working groups

The 'archive' for completed work and records

A centre for online multidisciplinary discussion

A resource to be interrogated by existing or potential new partners

Deliverables

D6 – Virtual Knowledge Park

Milestones[16] and expected result

Effective working groups

Posted reports in due time

Dissemination of multidisciplinary information and updates in a timely fashion between related groups

[16] Milestones are control points at which decisions are needed; for example concerning which of several technologies will be adopted as the basis for the next phase of the project.

Workpackage description (full duration of project)

Workpackage number	WP7	**Start date or starting event:**				Month 36
Participant id	5	2	3	4	1	
Person-months per participant	1	1	1	1	1	

Objectives

Website

Description of work

Information taken and summarised from VKP to give a clear overview to the non-specialist or lay person as to the relevance of the project, its key actions and important results

Information as to members who may be approached for further information

The 'public face' of the project

Deliverables

A working website

Monitoring of number of 'hits'

Milestones[17] and expected result

[17] Milestones are control points at which decisions are needed; for example concerning which of several technologies will be adopted as the basis for the next phase of the project.

Workpackage description (full duration of project)

Workpackage number	WP8	**Start date or starting event:**				
Participant id		1	2	3	4	5
Person-months per participant		2	5	3	3	3

Objectives

Book

Description of work

A multidisciplinary textbook allowing wide dissemination of up to date, research and evidence based knowledge

Deliverables

D7 – Book

Milestones[18] and expected result

Publication arrangements and typescript complete by end of SSA

[18] Milestones are control points at which decisions are needed; for example concerning which of several technologies will be adopted as the basis for the next phase of the project.

Workpackage description (full duration of project)

Workpackage number	WP9	**Start date or starting event:**				
Participant id		2	3	4	5	1
Person-months per participant		20	20	20	20	1.5

Objectives

Workgroups

Description of work

Face to face discussion for management and support activities concerning the project as a whole (Executive Board) and specific aspects (interdisciplinary and single-displinary thematic working parties). Although much can be achieved by the VKP, the scope of the collaboration is such that protected time and face to face discussion is key to maintaining the impetus, appropriate focus and to consider areas for further development.

Person-months include all preparatory/follow-up activities for meetings

50% of the work covers Support Activities, 50% covers Management Activities

Deliverables

Milestones[19] and expected result

Updating and reporting through VKP, website and Annual Meetings so that all group members are kept fully updated and informed

[19] Milestones are control points at which decisions are needed; for example concerning which of several technologies will be adopted as the basis for the next phase of the project.

Workpackage description (full duration of project)

Workpackage number	WP10	**Start date or starting event:**				
Participant id		1	2	3	4	5
Person-months per participant		1	1	1	1	1

Objectives

Final Report

Description of work

Bringing together a full evaluation of all aspects of the performance of the SSA in the defined format required by the Commission

Deliverables

D8 – Final Report

Milestones[20] and expected result

[20] Milestones are control points at which decisions are needed; for example concerning which of several technologies will be adopted as the basis for the next phase of the project.

B.7 Ethical, safety and other EC-policy related issues

Ethical, legal, social and safety issues

The European Commission's web site provides the following definition: "*The Commission considers sensitive ethical issues to be those which:*

- *involve human beings, for example, in clinical trials;*
- *use human tissues, in particular embryonic and foetal tissue;*
- *use animals, in particular, genetically modified animals and non-human primates;*
- *data production.*"

The Special Support Action instrument of FP6 covers the funding of "*Conferences, Seminars, Studies and analysis, Working and Expert Groups, Operational support and dissemination, Information and communication*". Funding of the research work itself is not included in the list, and accordingly this proposal does not include any research work. For this reason, ethical considerations related to proposed research work are not relevant to this proposal, and accordingly all of the questions of Section B.7.1 a) headed "*Does your proposed research involve*" have been answered with "not applicable".

The DASIM proposal has an indirect connection to research ethics issues through the research work which will be managed, discussed, planned and disseminated in the DASIM Work Program. This research work has been or is being funded from other sources as a result of approval of research funding proposals in which ethical issues were taken into account. Thus ethical issues concerning this research have already been examined and approved by the competent national or international authorities.

The DASIM proposal may also have an indirect connection to research ethics issues in that a possible of DASIM activities may be a future proposal for research funding. Ethical issues related to such a future proposal will be addressed at that time.

However, the DASIM proposal will involve the exchange of data obtained through measurements of patient sample materials, and this falls under the scope of "*Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data*". In this context, we confirm that the DASIM Work Program will under no circumstances involve the dissemination of patient medical records or other data in a form which allows identification of the individual to which it pertains. All data disseminated within the framework of the DASIM Work Program will be fully anonymized. The DASIM work program will not involve storage, processing or dissemination of any 'personal data' as defined in Article 2 Section (a) of Directive 95/46/EC.

An important social issue of relevance to this proposal is the potential impact of the proposal on the costs of health care. This issue is discussed in Section B.2.

Other EC-policy related issues

1. PUBLIC HEALTH

In the field of public health, European Commission policy documents identify cancer, cardiovascular disease, communicable diseases including TSEs and women's health as issues of sufficient importance to require position statements, strategy and action plans at the Commission level. The present proposal directly addresses these issues by including the named areas amongst our top priorities for improvement in the accuracy, speed and information content of diagnosis by introduction of new technologies.

2. RESEARCH AND INNOVATION

In the Commission document "Towards a European Research Area", the Objective statement includes: "*To create a European area the purpose of which is to establish a border-free zone for research, in which scientific resources will be better deployed*". The coordination and structuring activities of the DASIM proposal are intended to serve precisely this purpose, and are consistent with many of the more detailed policy objectives mentioned in this document.

3. SIXTH FRAMEWORK PROGRAM

The Introduction to the policy area "Research and Innovation" includes the following general introduction to FP6:
"*The new proposal is a deliberate break with past FPs with regard to ambition, scope and the instruments to be used in its implementation. The aim is to achieve greater focus on questions of European importance and a better integration of research efforts on the basis of an improved partnership between the various actors in the European Research Area. This initiative also aims at providing the Union with a genuinely common strategy designed to strengthen Europe's scientific and technological dynamism on an increasingly global stage.*"
The DASIM proposal harmonizes with these stated aims. There is a specific focus on a theme already identified in the Call as one of the questions of European importance, with the objective of achieving a better integration of research efforts through improved partnership. The proposal is an element in the creation of a common strategy with respect to the utilization of the member states' large scale science facilities in this priority research field.

4. INFORMATION SOCIETY

The introduction to this policy area states amongst the policy objectives: "*stimulating research into the development and deployment of new information and communication technologies*". Through the Virtual Knowledge Park as detailed in Work Package 5, this proposal will deploy state-of-the-art information and communication technology as an essential tool to allow the proposal to achieve its coordination and structuring goals, as well as to disseminate information to the medical profession.

B.7.1 Ethical aspects

a) Specify if your project involves:

Does your proposed research involve:	YES	NO
• Human beings	Not applicable, no research is proposed	
Persons not able to give consent	Not applicable, no research is proposed	
Children	Not applicable. no research is proposed	
Adult healthy volunteers	Not applicable, no research is proposed	
• Human biological samples	Not applicable, no research is proposed	
Human embryonic stem cells in culture	Not applicable, no research is proposed	
Human foetal tissue/human foetuses	Not applicable, no research is proposed	
• Personal data or genetic information	Not applicable, no research is proposed. Our proposed coordinating and structuring activities do not involve personal data or genetic information	
• Animals (any species)	Not applicable, no research is proposed	
Transgenic animals	Not applicable, no research is proposed	
Non- human primates Dogs, pigs, cats,	Not applicable, no research is proposed	

b) Confirm that the proposed research does not involve:

- research activity aiming at human cloning for reproductive purposes,
- research activity intended to modify the genetic heritage of human beings which could make such changes heritable[21],
- research activities intended to create human embryos solely for the purpose of research or for the purpose of stem cell procurement, including by means of somatic cell nuclear transfer,
- research involving the use of human embryos or embryonic stem cells with the exception of banked or isolated human embryonic stem cells in culture[22].

The proposed research does not involve any of the issues listed in point B.7.1.b)	**CONFIRM** **No Involvement**
	Not applicable, no research is proposed

[21] Research relating to cancer treatment of the gonads can be financed.

[22] Proposers should note that the Council and the Commission have agreed that detailed implementing provisions concerning research activities involving the use of human embryos and human embryonic stem cells which may be funded under the 6th Framework Programme shall be established by 31 December 2003. The Commission has stated that, during that period and pending establishment of the detailed implementing provisions, it will not propose to fund such research, with the exception of the study of banked or isolated human embryonic stem cells in culture.

B.8 Gender issues

B.8.1 Participation of women

Answer the following questions:

- Are there women directly involved:
  - in the scientific management of the project? Yes
  - in the scientific partnership as scientific team leader in the project? Yes
- % of women scientists involved in the project[23]:
  - ⇒ Early researchers (less than 4 years after graduate)? 35 %
  - ⇒ Experienced researchers (minimum 4 years after graduate or having a PhD)? 31 %
- Comment and justify if necessary

FP6 Specific Support Actions do not provide any funding for the appointment of research staff, therefore it is not possible for the DASIM proposal to exert any direct influence on the proportion of women employed in science at any level.

Similarly, it is not possible for the DASIM proposal to exert any influence on the proportion of women involved in the project. The guiding principle for the selection of the team to carry out a project of this kind has to be dictated by the areas of expertise needed. For example, it is regrettable that only 2 out of Europe's 13 IR beamline scientists are female, but nevertheless this imbalanced group must be included in the project in its entirety if the project is to succeed - because the aim of networking existing research only makes sense if all such research is covered, networking only some of the research is not helpful. The percentage of women involved in the project is thus dictated by the percentage of women amongst the tenure of the positions whose participation is required.

- Do you plan specific measure(s) regarding women role/participation in your project? Which? How? When?

Within the limits of an SSA as discussed above, influence can only be exerted at the level of the inclusion of female project participants in the scientific management of the project. The membership of the Executive Board and other decision-making bodies tends to come about through proposals made in preceding decision-making bodies, with a certain element of calling for volunteers. The DASIM proposal plans to monitor the proportion of women amongst the proposed membership of every such scientific management body. If the proposed female participation is too low, a targeted search for suitably qualified women amongst the project participants will be carried out. Where necessary, suitably qualified women will be approached directly and encouraged to volunteer as participants in the management body.

[23] Definitions according to the FP6 mobility & Marie Curie activities.

B.8.2 Gender aspects in research

Answer the following questions:

	Yes	No
• Does the project involve human subjects?		NO
• Does the project use human cells / tissues / other specimens?		NO
• If human subjects are not involved or human materials not used, does the research involve animal subjects or animal tissues / cells / other specimens *(as models of human biology/physiology)* in such a way that it is expected that may have implications for humans?		NO
• Does the project use collection of data related to human subjects, human materials, animal subjects or animal materials	YES	

A positive answer to any of these questions implies that gender/sex aspect should be taken into consideration in the research proposal.

	Yes	No
Are gender/sex differences with respect to the research documented in the literature?	YES	

If yes please give details.

The research documented in the literature covers gender-specific serious diseases such as breast, cervical and prostate cancer.

A negative answer to this question may imply some innovation in the proposal towards this issue that will be taken into account in the evaluation process.

If there are gender/sex aspects in your project:

- Detail the questions addressed in their proposal related to gender/sex aspects in research.
- Comment on the expected outcome.
- Describe how the gender/sex aspects will be taken into account in the research, methodology and interpretation of their results.

If you do not consider gender/sex differences, provide justification.

- *The evaluation panel will assess the relevance of the justifications provided.*
- *Neither additional costs, nor difficulties in obtaining female cells, female tissues, female specimens, or recruiting female subjects, would not normally be considered as a valid reason for excluding gender/sex aspects ("female" includes both animal and human subjects).*

It is not to be anticipated that there will be any gender differences pertaining to the feasibility of obtaining diagnostically relevant information by synchrotron infrared microspectroscopic examination of patient cell and tissue specimens.

However, it is certainly the case that the feasibility of the above-mentioned undertaking depends on the disease to be diagnosed. Thus the relevant literature pertaining to both synchrotron light sources and benchtop infrared microscopes has covered a very wide range of indications. One aim of the DASIM proposal will be to compare data and to critically examine the potential of the technique on a per-disease basis, with the aim of identifying those diseases where infrared microspectroscopy shows most promise as a diagnostic tool,

and to propose these as areas of research priority, in particular in the final report, as specific recommendations for research funding in the future Framework Program.

The issue of identifying research priorities in the sense of individual diseases is a gender issue because some of the most serious diseases are gender specific. The DASIM proposal takes this issue into account, and therefore includes serious gender specific diseases such as breast, cervical and prostate cancer amongst those to be evaluated as potential priority areas.