European Cooperation in the field of Scientific and Technical Research - COST -

Brussels, 21 November 2012

BM1205

MEMORANDUM OF UNDERSTANDING

Subject :	Memorandum of Understanding for the implementation of a European Concerted Research Action designated as COST Action BM1205: European Network for Skin Cancer Detection using Laser Imaging

Delegations will find attached the Memorandum of Understanding for COST Action as approved by the COST Committee of Senior Officials (CSO) at its 186th meeting on 20 - 21 November 2012.

MEMORANDUM OF UNDERSTANDING
For the implementation of a European Concerted Research Action designated as

COST Action BM1205
EUROPEAN NETWORK FOR SKIN CANCER DETECTION USING LASER IMAGING

The Parties to this Memorandum of Understanding, declaring their common intention to participate in the concerted Action referred to above and described in the technical Annex to the Memorandum, have reached the following understanding:

1. The Action will be carried out in accordance with the provisions of document COST 4154/11 "Rules and Procedures for Implementing COST Actions", or in any new document amending or replacing it, the contents of which the Parties are fully aware of.

2. The main objective of the Action is to coordinate efforts and enhance interactions of researchers, as well as to promote development and application of early, accurate diagnosis of skin cancer known to be the key determinant of patient outcome.

3. The economic dimension of the activities carried out under the Action has been estimated, on the basis of information available during the planning of the Action, at EUR 52 million in 2012 prices.

4. The Memorandum of Understanding will take effect on being accepted by at least five Parties.

5. The Memorandum of Understanding will remain in force for a period of 4 years, calculated from the date of the first meeting of the Management Committee, unless the duration of the Action is modified according to the provisions of Chapter V of the document referred to in Point 1 above.

A. ABSTRACT AND KEYWORDS

The Action will provide an interdisciplinary framework to enhance interaction activities within the field of optical biosensing, between world-class academic groups, labs and system integrators from industry. It will exploit novel laser sources and innovative feedback interferometry in specific biomedical applications. Recent developments in the design of solid-state laser sources at near-infrared, mid-infrared and terahertz frequencies, coupled with novel self-mixing approaches to signal detection and the integration of these into imaging platforms, provide a way forward in the design of the next generation of detection systems. Specifically, it is proposed to extend the non-invasive interrogation of skin tissue into these frequencies. The Action will exchange knowledge, explore and compare technology platforms and perform clinical validation and evaluation of new devices which will permit detection of both the changes in skin lesions and disordered blood flow patterns and tissue perfusion typical of malignancy. The COST Action is an ultimate choice for this network as it will bring together COST countries academia, industry and clinical end-users which would be virtually impossible through any other European funding mechanism.

A.2 Keywords: Early cancer diagnosis, Medical imaging of Skin Cancer, Infrared and Terahertz imaging, Optical feedback Interferometry, Laser Self-Mixing sensors

B. BACKGROUND

B.1 General background

The exchange of knowledge and development of innovative approaches to biosensing problems such as the non-invasive detection of skin cancer are key issues to be addressed if we are to move to the next generation of detection systems. Optical sensing solutions directed at skin cancer detection in human clinical practice are significant issues at present. Early detection, in the case of melanomatous skin cancer, is the only factor to have reduced mortality in the last forty years in Western societies. The existing base of diagnostic instruments is however, solely based on detection of the morphological features of skin lesions seen by visible light at low magnification. Surveys of published clinical data reflect the plateauing of performance measures using existing technology and call for newer approaches to enhance sensitivity and resolution. The search for investigative non-invasive optical techniques remains directed at a suite of methods which can augment the current success of direct visible magnification and improve on the existing sensitivity, specificity

and breadth of diagnosis. Alternative (non-optical) investigations such as magnetic resonance imaging and ultrasound imaging are either expensive, of poor sensitivity and/or inappropriate for rapid population screening and office diagnosis. The leap to general adoption of non-visible wavelengths and diagnostic features based on the function of tissue has been prevented largely through absence of a compact, inexpensive sensing solution. Lasers have shown promise in a variety of diagnostic roles, but the complexity of the existing systems have seen them being used as research tools at best.

The recent developments in self-mixing interferometry (SMI) whereby the sensor source also acts as the detector have clearly demonstrated its benefits in terms of cost, size and robustness. Adopting the self mixing (SM) model as a technical foundation stone, the Action will develop ideas and perform collaborative activities in the framework of already well funded research centres, towards a suite of novel sensors ultimately able to be combined as a diagnostic system for non-invasive in vivo applications. This achievement will constitute a significant breakthrough in both technical and clinical terms and will overcome the current bottleneck of basing skin cancer detection devices solely on visible light contrast measures.

Why COST:

The collaborating academic groups and industrial system integrators here, working in related areas across Europe and Australia (through COST Australia Reciprocal agreement mechanism), would come together to enhance the opportunity of participating in a significant development in both the fundamental science of biophotonics as well as advancing the state of the art in cancer diagnostics. The proposed Action participants are fortunate in being able to access the state of the art facilities for novel quantum-cascade and vertical-cavity surface-emitting lasers design, fabrication and characterisation in Europe and Australia which provide the technological platform, as well as expertise and resources of a clinical end-user group. The dermatology research groups involved in the network have a world-recognised profile in assessment of dermatoscopic approaches to skin cancer detection and provide the dual benefit of end-user feedback in the design and development phases, as well as the hosting of validation trials in the assessment phases. Enhancing this existing cross-disciplinary collaboration through an intergovernmental framework as it is COST is therefore critical to the progress of non-invasive optical sensing technologies for this class of disease. Within the framework of the Action, communications between researchers using complementary types of investigations will be promoted, in contrast with the present situation where fruitful scientific efforts are obstructed by poor connections and the lack of collaboration between various studies which require interdisciplinary skills.

B.2 Current state of knowledge

It is well recognised that fast, early diagnosis in the case of melanoma skin cancer is the only factor to have reduced mortality in the last forty years in Western societies. The existing base of diagnostic instruments is however, solely based on detection of the morphological features of skin lesions seen by visible light at low magnification. It is also well recognised that the varied nature of cancer is best detected using a variety of approaches from simple morphology (appearance) to the aberrant tissue and cellular function (blood flow, expression of biomolecular markers).
Non-invasive monitoring and imaging in biomedicine has relied heavily on developments in photonics over the last thirty years. The imaging of structures within the superficial layers of the skin in particular, has become a predominant technique in detecting a number of skin conditions in the developed world. This is despite the poor contrast seen in the visible spectrum when attempting to detect nonmelanoma cancers (NMC) such as basal cell carcinomas (BCC) and squamous cell carcinomas (SCC). Although uncommon, studies have shown the viability of discriminating cancerous lesions from those of a benign nature on the basis of the spectral absorption largely due to endogenous chromophores.
Hand-held magnification and reduction of stratum corneum diffraction through oil immersion is the basis of conventional dermoscopy. The dermatoscope is principally a visible spectral tool, although augmentations allowing use of NIR wavelengths have resulted in superior sensitivity in the detection of melanoma. The advantage seen in dermatoscopes with extended wavelengths is achieved algorithmically, not optically. The derived images which show tumour invasion at depths below the basement membrane are the means by which the advantage is conferred.
Optical Coherence Tomography (OCT) relies on the reflectance of weakly coherent light from skin structures which in turn is interferometrically detected. A magnitude and depth signal of the scattering structure is able to be determined. This technique may achieve a resolution of 1 µm and in an imaging mode, can show structural features in skin. Images produced from 2D vertical slices have no contrast derived from cellular features and it is not therefore able to assist in the early detection of melanoma. Confocal Scanning Light Microscopy (CSLM) in reflectance mode has enjoyed some success in investigation of skin cancer. The technique based on detection of reflected light from in-focus planes within the tissue is limited by the wavelength of the excitational laser used. Typical penetration depths of 100 µm are seen and contrast from pigmented and non-pigmented melanosomes has been reported using near infrared sources. These devices are not portable and are principally used as research tools at the present time.

The search for investigative non-invasive optical techniques aimed at *in vivo* detection of skin cancers (both melanotic and nonmelanotic) remains directed at a suite of techniques which can augment the current success of direct visible magnification and improve on the existing sensitivity, specificity and breadth of diagnosis. Alternative (non-optical) investigations such as magnetic resonance imaging (MRI) and ultrasound imaging are either expensive, of poor sensitivity and/or inappropriate for rapid population screening and office diagnosis. A broader optical solution would ideally enhance depth of interrogation and provide information based upon additional means of contrast between normal tissue and pre-cancerous tissue in a safe, robust fashion. The option of ultimately being a portable office diagnostic tool should also be considered as an important criterion in selection of technical approaches.

Laser sources offering high brilliance and coherence have shown promising results in a variety of diagnostic roles, but the complexity of the source and particularly the intricacy of an interferometric detection scheme have seen such diagnostic systems being used as research tools at best. The recent developments in *self-mixing interferometry* (SMI) whereby the sensor source also acts as the detector have clearly demonstrated its benefits in terms of cost, size and robustness. An adoption of this detection approach here can enable broader interrogation of tissue than simply visible morphology with all of the technical advantages the SMI approach delivers.

SMI is an ideal common platform which can enhance the capabilities of existing laser diagnostic approaches. In order to optimize the discriminatory power of any sensing system applied to this problem it is best to seek differing modes of characterization in order to capture the multiple means by which cancerous behaviour may be expressed in skin tissue. Three candidate approaches have been identified for this purpose. Firstly, imaging and measurement of blood flow at the capillary scale is an ideal means of detecting so-called *neovascularisation* or the increase in disordered blood vessel growth stimulated by a variety of cancers. Secondly, at the *molecular level*, specific classes of biomolecules have been observed which are associated with cancer gene expression in skin cells. Examples of such molecular complexes are polyphosphids and amides whose spectral signatures in the mid infrared region of the spectrum have been shown to undergo significant variations that will be considered here. Lastly, the *bulk-optical properties* of skin tissue that have been observed to change in cancer, such as the complex permittivity (refractive index and absorption), have been previously shown to be of discriminatory value at terahertz (THz) frequencies. Indeed THz radiation is known to be highly sensitive to changes in both chemical and physical structure. The adoption of a THz interrogation sub-system is therefore also proposed.

B.3 Reasons for the Action

The leap to general adoption of non-visible wavelengths and diagnostic features based on the function of tissue has been prevented largely through absence of a compact, inexpensive sensing solution. Surveys of published clinical data reflect the plateauing of performance measures using existing technology and call for newer approaches to enhance sensitivity and resolution. Adopting the self mixing (SM) model as a technical foundation stone, the coordinated Action will enable the development of a suite of sensors ultimately able to be combined as a diagnostic system for non-invasive *in vivo* applications. The technical tasks will be directed at integration of the sensors through the common SM approach and development of support electronics and signal processing. This achievement will constitute a significant breakthrough in both technical and clinical terms and will overcome the current bottleneck of basing skin cancer detection devices solely on visible light contrast measures.

B.4 Complementarity with other research programmes

Members of the Action have participated in a number of recent European funded complementary programmes. Good examples are: ‘New opportunities in terahertz engineering and science (NOTES)' and 'Terahertz Optoelectronics: from the science of cascades to applications(TOSCA)' both European Research Council funded grants; ‘Microwave and Teraherz Photonics (MITEPHO) an ITN Project; "French-Australian Science and Technology (FAST) International Science Linkages Program"

C. OBJECTIVES AND BENEFITS

C.1 Aim

The main objective of this Action is to coordinate efforts and enhance interaction of researchers, as well as to promote development and application of early, accurate diagnosis of skin cancer known to be the key determinant of patient outcome.

C.2 Objectives

- Development of VCSEL Array blood perfusion imaging
- Assessment of Tissue characterization at mid-infrared (MIR) in reflectance mode
- Tissue characterization at terahertz (THz) frequencies
- Validation and evaluation of combined sensing modalities

C.3 How networking within the Action will yield the objectives?

The application of current SMI knowledge and the development of our understanding of SMI physics will be applied to all three technical plans. This synergistic approach to the research problems will enhance the capabilities of the individual techniques, serve to accelerate the research timeline and ultimately generate cost and manufacturing efficiencies for a diagnostic instrument which may be based on these concepts.
The Action will bring together researchers from a number of European countries and partners from Australia through COST Australia Reciprocal agreement mechanism (and others who join the Action at a later stage) with diverse expertise to discuss the specific projects, formulate innovative solutions to problems, establish the most appropriate collaborations, and execute their plans through COST instruments including Short Term Scientific Missions (STSMs). The Action will increase cohesion between scientists working in the field in Europe and Australia to progress significantly by creating and efficiently disseminating new knowledge and provide good visibility of COST. Networking through Working Group meetings and STSMs will enable this communication by providing (1) a forum for cross-pollination of ideas and dissemination of best practice; (2) opportunities for interaction between academic labs, industrial system integrators and clinical end-users which will ensure that the scientific strategies followed will be suitable for subsequent exploitation; (3) training opportunities for Early Stage Researchers to learn the scientific language of other disciplines while gaining practical and theoretical experience of techniques outside their own discipline. The Action will encourage applications for Initial Training Networks reflecting the

aims of the Working Groups, and support Early Stage Researchers to apply for Marie Curie Intra-European Fellowships within the network to maximise their contribution to achieving the objectives, while allowing them to develop as independent scientists. The STSMs will allow researchers to access the state-of-the-art equipment base that is spread across the participant's laboratories and will contribute to strengthen the network by allowing, especially young scientists, to improve their skills and achieve an interdisciplinary approach.
Expected deliverables include: development of stable collaboration lines, presentation of European projects, joint publications, etc. The Summer School for young researchers in tissue imaging and technology for melanoma early diagnosis will be organised once per year in conjunction with annual Action meeting. Workshops will be organized periodically or as part of scientific conferences (topical sessions) or international events where result from COST participants will be disseminated promoting COST networking policy. Their principal scope will be the merging of the different communities (academic research teams, industrial based imaging system integrators and clinical end-users) reporting on their respective achievements and targeting the advancement of the Action. During the workshops, an open forum will be created for the benefit of all participants, internal and external to the COST community.

C.4 Potential impact of the Action

Expected impact can be summarised as:
(1) New knowledge of the changes in optical properties of tissue in skin cancer; (2) Objective estimates of the performance of sensors based on novel techniques; (3) Potential platform for commercial medical device manufacturers; (4) Formalisation and consolidation of existing and new academic relationships which will lead to future collaborative ventures; (5) Incorporation of Australian partners expertise in techniques which are not readily available to European partners; (6) Access to world-class validation trial centre and their clinical end-user group for design feedback; (7) Long-term European community health benefits of improved cancer screening; (8) A new generation of young researchers will be equipped with the confidence and expertise to cross traditional scientific boundaries thus enabling them to become future leaders of the field.

C.5 Target groups/end users

The Action is highly focused and the activities of the partners are complementary. This Action brings some of the partners together to work on a specific topic for the first time and established relationships will be consolidated. The Action has a clear European dimension for a number of reasons. One of the most important of these relates to the target application area: that of the developing a sensing system for skin cancer diagnostics. The goal of reducing cancer deaths is confluent with stated European policy, and technological leadership available herein will make this goal achievable.

The exploitation of Action results will be carried out through various means. The academic partners will exploit the research effort in their education process. Several PhD theses are expected to be generated directly or indirectly from the results of the Action research. Industrial partners were involved or have all been consulted during the preparation of the proposal and they intend to make use of the results of this activity to significantly strengthen their market positions. The goals of the Action are well aligned with their business strategy to explore new markets related to optical sensing technologies. For example, industrial system integrators will exploit the results of the proposal by providing SMI-MIR QCL emitters for a wide variety of applications including medical sensing, safety measures and imaging technologies, in which MIR radiation is required.

The Action will feed the European growth in this emerging bio-medical imaging technology, and see the exploitation of developed self-mixing interferometry applications in a range from near infrared to terahertz frequencies for decades to come. In this way, Action will enable Europe not only to maintain, but also enhance, the leading position of European industry in high-value photonic products for bio-medical applications. The objectives of the Action will benefit a wide range of target groups from academic researchers (new tools for understanding physics and application on bio-sensing), through industry (improved methods for making medical imaging system) and clinicians (tools for diagnosis of melanoma) to patients as the ultimate end-users.

D. SCIENTIFIC PROGRAMME

D.1 Scientific focus

In order to optimize the discriminatory power of any sensing system applied to this problem it is best to seek differing modes of characterization in order to capture the multiple means by which cancerous behaviour may be expressed in skin tissue. Three candidate approaches, already

intensively explored between key Action's partners, have been identified for this purpose. Firstly, imaging and measurement of blood flow at the capillary scale is an ideal means of detecting so-called neovascularisation or the increase in disordered blood vessel growth stimulated by a variety of cancers. Secondly, at the molecular level, specific classes of biomolecules have been observed which are associated with cancer gene expression in skin cells. Examples of such molecular complexes are polyphosphids and amides whose spectral signatures in the mid-infrared region of the spectrum have been shown to undergo significant variations that will be considered here. Lastly, the bulk-optical properties of skin tissue that have been observed to change in cancer, such as the complex refractive index, have been previously shown to be of discriminatory value at THz frequencies. Indeed THz radiation is known to be highly sensitive to changes in both chemical and physical structure. The adoption of a THz interrogation sub-system is therefore also aimed. Although neovacularisation may be a delayed response to internal cancers, the presence of aberrant blood vessels in the superficial skin cancers we propose studying evolve along with the tumour. This is evidenced by the reliance on visible detection of vascular patterns as a principal diagnostic feature in conventional dermoscopy.

Four Working Groups will address the topics briefly described in the scientific work plan:
- WG 1: VCSEL array perfusion imaging
- WG 2: Tissue characterization at mid infrared frequencies using Quantum Cascade Lasers (QCLs)
- WG 3: Tissue characterisation at terahertz frequencies using THz QCLs SMI.
- WG 4: Validation and evaluation of combined sensing modalities

D.2 Scientific work plan methods and means

1. Development of VCSEL Array blood perfusion imaging

The Action will develop an ultra-compact sensing technology based on the self-mixing interferometer that uses Vertical-Cavity Surface-Emitting Laser (VCSEL) arrays both for the emission and the detection of light. This technique has high sensitivity, high signal to noise ratio, high spatial resolution, simple optical design, low power consumption (portable system), potentially low cost and the significant advantage of possible implementation in massive two-dimensional arrays.

Self-mixing interferometry, on which this objective is based, is an acknowledged new technique for detection of small displacements, change in the refractive index of materials, and particle flow. The

self-mixing phenomenon occurs when the laser beam is partially reflected from an external target and injected back into the laser cavity. The reflected light interferes or 'mixes' with the light inside the laser cavity and produces variations to the threshold gain, emitted power, lasing spectrum and the laser terminal voltage. This phenomenon allows the laser to be used as an interferometric sensor incorporating the light source and the interferometer in one device thus significantly reducing the cost and the complexity of the sensing system. The homodyne (coherent) detection nature of this sensing scheme inherently provides very high sensitivity (at the quantum noise limit) and consequently suffers minimal crosstalk between the channels in a free-space multichannel implementation. The design of Vertical-Cavity Surface-Emitting Laser (VCSEL) devices and arrays has not been expressly pursued for this proposal. Experimental work and commercial products to date, have relied on pre-existing devices sourced from manufacturers for communications applications. As such, the performance of any sensor system based on VCSEL devices is ultimately limited. As part of this technical objective, the modelling of the self-mixing effect and related device physics will be required to expand the current single-beam technology to 2D and possibly 3D imaging (depth sectioning) based on two-dimensional VCSEL arrays.

2. Assessment of Tissue characterization at MIR in reflectance mode

The Action will develop an MIR reflectance imaging technique exploiting the phase and power sensitivity of SMI when the feedback radiation derives from quasi-static targets. The use of different wavelengths tuned to specific molecular resonances, relevant for diagnosis of skin lesions, will make available additional chemical mapping to the vascular and structural information provided by VCSEL arrays and THz imaging.

The mid-infrared (MIR) region (2-10 μm) is well known to spectroscopists and biologists as the "molecular fingerprint region" because of the rich variety of C-H-N-O related stretching modes having signatures in this portion of the electromagnetic spectrum. With respect to the near-infrared (NIR) (0.8 - 2 μm) wavelengths, MIR radiation in biological tissues experiences a larger absorption and a reduced scattering. While the former is the main cause of the shallow penetration of the MIR radiation in water rich substances, the latter is a desirable attribute for any imaging application. The low MIR photon yield in biological materials, together with the lack of coherent (high brilliance) sources, has limited in practice the exploitation of MIR frequencies to absorption spectroscopy. In spite of the valuable information provided by spectrally resolved absorption measurements, the requirement of sample preparation (samples must be thinned down to a hundred microns) and of a separate detector that must be placed at the opposite side of the specimen, make this technique impracticable for *in vivo* diagnosis.

Laser-based MIR reflectance imaging of biological tissues has been recently demonstrated with

Quantum Cascade Lasers (QCLs). Widely tuneable (suitable for wavelength multiplexing), MIR-QCLs are now available at several central wavelengths from a variety of commercial suppliers. They operate at room temperature, or are thermoelectrically cooled, and have already demonstrated their sensitivity to self-mixing also in relation to chemicals absorption measurement.
The sensitivity of SMI detection applied to the high power MIR-QCL available sources will allow for tissue characterization in reflectance mode, the only practical scheme for in vivo diagnosis.

3. Tissue characterization at THz ~~frequences~~frequencies

The Action will develop an imaging system based on the self-mixing effect in terahertz QCLs for simultaneous readout from plurality of lasers operating at different wavelengths.
The last 10–15 years have witnessed a remarkable growth in the field of terahertz (THz) science, which is maturing into a vibrant international research area drawing in researchers from across the physical and biological sciences. Historically, the development of compact high-power laboratory sources of THz frequency (0.1 – 10 THz) radiation, as well as compact and sensitive THz detector technologies, has presented an enormous challenge owing to the difficulties of extending either existing electrical or optical technologies into the THz range. Nevertheless, THz radiation has attracted particular interest for the development of new imaging and sensing technologies due to its non-ionising nature, and its ability to discriminate samples chemically, to identify differences in physical and chemical structure, and to penetrate materials that are visibly opaque. Potential applications are therefore numerous and include: Material characterisation ; chemical sensing; biomedical imaging; non-invasive inspection; and pharmaceutical monitoring.
A superficial skin imaging system based at THz wavelengths has an innate advantage of wider field coverage and the ability to characterise tissue structure at the expense of resolving cellular structure that may not be essential for the histological diagnosis of most cancers. The properties of cancerous tissue with respect to its optical interactions at THz wavelengths are only now being explored. Initial work by participant of this Action and co-workers shows potential for this technique in discriminating common basal cell carcinoma (BCC) from surrounding healthy tissue. In this series of 15 cases THz contrast always exceeded visible contrast upon which the conventional imaging diagnosis is made. Clearly, the molecular composition of cancerous tissue will differ, giving rise to differing vibrational modes within the THz range, and thereby a contrast in complex permittivity. The orientation of micro-structure (i.e. fibre orientation, cellular arrangement) is also perturbed in tumours, which can be detected through measurement of the interaction of THz irradiation at varying angles. The exact nature of these spectral and angular responses of various cancer types to THz interrogation are as yet unknown, but are clearly of great value as the basis for discrimination tools for non-invasive *in vivo* THz imaging of human skin.

The challenges associated with terahertz imaging and spectroscopy are *dual*, and are principally related to technological developments of THz sources, and appropriate detectors. Nevertheless, in recent years the THz quantum cascade laser (QCL) has attracted much interest as a radiation source for THz imaging and sensing. THz QCLs are compact semiconductor heterostructure devices capable of continuous-wave emission at powers exceeding 100 mW. Narrowband emission has been demonstrated in these sources at frequencies between 1.2 to 5.0 THz, and at operating temperatures as high as 200 K in pulsed mode. Real-time imaging in both a transmission and reflection geometry has also been demonstrated at near-video-rates (20 frames per second) through use of a microbolometer focal-plane array with a THz QCL source. Other detector systems employed for THz imaging and sensing include room-temperature Schottky diodes Golay cells, pyroelectric detectors and cryogenically-cooled bolometers. Whilst room-temperature detectors avoid the reliance on cryogenic liquids, their response is typically slow and sensitivities are significantly poorer than those achievable with cryogenically-cooled bolometric detection.
The Action aims here that an imaging system based on the self-mixing effect in terahertz QCLs be developed for simultaneous (concurrent) readout from plurality of lasers operating at different wavelengths, by using an array of QCLs *as both the THz source array and the sensor array*. The radiation emitted from each laser in the array will illuminate one spot on the sample/skin, and be reflected back into the same laser to create the self-mixing signal. The SM signal will be detected by sensing the change in QCL terminal voltage caused by the light scattered from the tissue and injected back into the laser, rather than using the signal from an independent (pyroelectric or bolometric) detector array.
The system will have all the benefits of THz imaging with bolometric arrays, with the additional benefit of higher sensitivity, higher spatial resolution, compact design and the advantage of simultaneous, parallel concurrent acquisition at several wavelengths providing for synergistic data fusion, thereby providing insight into both the micro-anatomical structure as well as the chemical composition of the constituent biomolecules.
4. Validation and evaluation of combined sensing modalities
The application and validation of the proposed sensing techniques will be directed in the three general areas of technical development as outlined in Technical Objectives 1, 2 & 3 above. Evaluation of the combination of the multiple investigative techniques in the discrimination of malignant versus non-malignant behaviour in tissue lesions will also be performed.
The overarching Action aim of providing a novel sensing system for skin cancer detection will be validated on the focussed clinical question of discriminating melanomatous skin cancers from benign, atypical lesions (naevi). This approach shadows in many ways the current focus in

automated decision making for melanoma detection using visible light morphological features only. Human validation studies are possible using existing recruited cohorts from studies being performed at UQ. Such populations are selected healthy adults with dysplastic naevi which may undergo malignant change to melanoma. Combined sensing of lesions using the three broad techniques proposed here will be performed. The development of a classifier, whereby an automated decision is made to classify a suspicious lesion as malignant or benign will be a subsequent step in the validation of the sensing approaches taken.

Firstly, the SM systems in the NIR, MIR and THz will be characterised on test targets for resolution and sensitivity on a range of wavelength specific targets. This will be required to optimise signal to noise ratios, determine spectral range, sensitivities and skin penetration depths. Secondly, characterisation of the microcirculation tissue phantoms, using microfluidic flow targets will be performed to determine accuracy of blood flow measurements, spatial resolution, signal to noise ratios and flow direction sensitivity. Finally, imaging and characterisation of *in vivo* lesions utilising sensors developed from the prior work will be conducted. This will be for the purpose of technical validation, end-user feedback and safety assessment only, and *no clinical trial status is intended* or implied for this work. No clinical management decisions will be made using any data derived from this step.

Specifically, the three sensor systems developed in from objectives 1-3 will enable the Action to:

- Acquire images in *three different ranges of the electromagnetic spectrum* while performing a *similar raster scan* of the sample using the self-mixing technique.

- Investigate the effect of absorption combined with the effects of blood perfusion (dynamic scattering) as well as scattering in superficial tissue layers. Measurement of hydration of stratum corneum (SC) is a tool frequently used in the pharmaceutical industry for analysis of transdermal drug delivery systems.

- Evaluate the benefits of image-fusion and contrast obtained using three different imaging modalities: THz reflection mode self-mixing imaging, MIR reflection-mode self-mixing imaging, and NIR functional self-mixing Doppler-perfusion imaging.

E. ORGANISATION

E.1 Coordination and organisation

The Action will be managed according to document COST 4154/11 “Rules and Procedures for implementing COST Actions”.
The Management Committee (MC) will be responsible for the following tasks:

1. Appointment of the Chair, Vice-Chair, Working Group (WG) leaders, an STSM manager and a website manager who will form the Core Group (CG) along with any other co-opted members at the discretion of the MC;

2. Budget planning and allocation of funds;

3. Plan MC and WG meetings, Action workshops and Training School events;

4. Coordinate interaction between Working Groups;

5. Evaluate and monitor the progress of the Action;

6. Promoting the Action to potential stakeholders and end users;

7. Host a concluding symposium involving all WGs.

The CG will be responsible for preparing annual and final evaluation reports. These reports will provide a mechanism by which the progress of the Action will be monitored. The CG will communicate with the COST Office and maintain the Action website. The website will be used to disseminate information for workshops and STSM applications among members of the Action, and have pages devoted to the activities of each working group, including links to joint publications for external dissemination of results, being also a powerful tool to further enhance COST visibility. Many of the scientific methods and bio-medical targets to be studied are relevant to more than one of the themed WGs, therefore joint WG meetings will be arranged to allow cross-pollination of ideas and maximise opportunity for forming productive collaborations. STSMs will be used to

enable exchange visits between participants, both within and between WGs. This scheme will be managed by the STSM manager assisted by a Steering Group (SG) comprising one representative from each WG. The SG will ensure a fair distribution of STSM funds across the Action with particular reference to gender balance and involvement of early stage researchers.

*Milestones***:** *Year 1*: setting up MC and WGs; determination of the WG meeting schedule; Creating website; launching the STSM scheme; *Years 2-4*: organisation of regular workshops; submission of joint applications for research funding; publication of joint papers arising from collaborations

E.2 Working Groups

The Action will be organised in four Working Groups (WG) as described in D. SCIENTIFIC PROGRAMME. Each working group will consist of several research groups. The WG leader appointed by the MC will be responsible for:

1. Actively representing the WG in the CG and MC;

2. Setting and monitoring milestones for the WG;

3. Providing the website manager with information about the WG;

4. Coordinating the organisation of WG meetings in collaboration with a local organiser;

5. Writing relevant parts of annual and final evaluation reports

Each WG will hold an annual workshop to discuss progress and plan future activities. A programme of joint meetings between complementary WGs will be used to encourage cross-WG collaboration.

E.3 Liaison and interaction with other research programmes

The MC will explore possibilities for joint workshops or symposia with other COST Actions with

complementary objectives, for example COST Actions, TD1003 “Bio-inspired Nanotechnologies: from concepts to applications”, MP1204 “TERA-MIR Radiation: Materials, Generation”, Interaction will also be sought with members of the Framework Programme 7 project CHARMING (Project reference: 288786).

E.4 Gender balance and involvement of early-stage researchers

The Action aims to achieve equal representation of men and women on the CG and SG. The SG will aim to allocate equal numbers of STSMs to men and women. Priority will be given to early-stage researchers when allocating STSMs. Equal numbers of male and female early-stage researchers will be encouraged to give oral presentations and chair sessions at all WG workshops. Training Schools will be coordinated with meetings involving all WGs to provide early-stage researchers with introductory lectures on experimental methods (e.g. laser design, growth and fabrication techniques, self-mixing interferometry, medical imaging of tissues, etc.) that are available within the Action.

F. TIMETABLE

The Action will last for four years. At the first MC meeting (year 1, month 1) the Chair, Vice-Chair, WG leaders, STSM manager and website manager will be elected. The website will be launched in month 2-3. Annual MC and CG meetings will subsequently coincide with annual Action workshops at which all WGs will be represented and external experts will be invited to promote discussion and interactions beyond the activities of the Action. These workshops will also double as mid-term and final review meetings for evaluating the success of the Action, and will have associated Training School events for introducing early-stage researchers to techniques out with their area of expertise. A round table discussing the sustainability of the Action deliverables will be also organised. WG meetings will be arranged between annual Action meetings. The MC will determine which combinations of WG should have joint meetings to ensure maximum opportunity for cross-WG collaboration. STSMs will run from the initial WG meetings until the end of the Action.

YEAR	1	2	3	4

ANNUAL MC/CG MEETING	X	X	X	X
WEBSITE LOUNCH	X			
ANNUAL ACTION WORKSHOP	X	X	X	X
TRAINING SCHOOL EVENTS		X	X	X
WG MEETINGS	X	X	X	X
STSM	XXX	XXX	XXX	XXX

G. ECONOMIC DIMENSION

The following COST countries have actively participated in the preparation of the Action or otherwise indicated their interest: BE,CH,DE,DK,ES,FI,FR,IE,IT,NL,RS,SE,UK. On the basis of national estimates, the economic dimension of the activities to be carried out under the Action has been estimated at 52 Million € for the total duration of the Action. This estimate is valid under the assumption that all the countries mentioned above but no other countries will participate in the Action. Any departure from this will change the total cost accordingly.

H. DISSEMINATION PLAN

H.1 Who?

The target audiences for dissemination of the results fall into three categories:
Target group 1. Academic, clinical and industrial researchers working in the fields of photonics, laser technology, biomedical imaging, dermatology, biological pharmaceutical who will be the immediate beneficiaries of the research output;
Target group 2. European and national policy makers who formulate funding strategy and calls for specific funding opportunities so that it will be possible to capitalise on the initial results arising from the activities of the Action;
Target group 3. The general public (including high school and undergraduate students) to stimulate open discussion about the opportunities that laser diagnostic, bio-photonics, medical imaging and cancer research can provide and excite young people in the subject to encourage them to choose these areas as a career option.

H.2 What?

- Scientific publications and review articles in high impact international journals, describing results of the work (target groups 1 and 2)

- WG meetings, including joint meetings with other Actions (target group 1)

- Action workshops with invited external expert speakers and lectures at key national/international conferences (target groups 1 and 2)

- The industrial partner will also use press releases and active promotion in technical advertisement-oriented journals (to advertise the achievements of the Action and to announce device/product launching at various stages of development

- Training School events and STSMs to allow early-stage researchers to learn and exploit new scientific techniques (target group 1)

- Undergraduate and postgraduate lectures at host institutions and schools visits (target group 3)

- Public engagement in science events (e.g., science festivals or Cafe Scientifique) (target group 3)

- Action website with public engagement pages, overview of each WG and links to published results (target groups 1-3), and with limited access pages for members of the Action (target group 1)

- Page on Wikipedia describing the Action linking to the Action website and with links from other Wikipedia pages on related topics (e.g., laser applications, bio-medical imaging, skin cancer, etc)

- Articles/interviews in the national media e.g., newspapers, radio, TV (target groups 1-3)

- A two-page 'COST Action Presentation' prepared by MC will prepare to be available for distribution at national/international meetings, and for those requesting further information about the Action activities.

H.3 How?

The MC will take responsibility for promoting the work of the Action and encouraging all members of the Action to participate widely in dissemination activities.

- *Action activities.* The WG meetings and Action workshops will be arranged in different geographical locations each time to encourage widespread participation. The STSM scheme and Training School events will be used to disseminate expertise within the Action and encourage the sharing of facilities for collaborative activities. World-leading external experts and members of strategic boards for European and national funding agencies will be invited to participate in Action workshops to promote awareness of our activities to key funding decision makers. Industrial representatives in relevant fields will also be invited to attend Action workshops to maximise opportunities for collaborative follow-on projects and enable feedback into the projects to ensure the research directions will be suitable for translation to final applications. All activities will be announced via an Action email list and information posted on the website.

- *Website.* The website will be a major focal point for disseminating information among members of the Action (password-limited access to internal pages), and externally (public pages describing the aims and results of each WG, and general information on the field for the general public). Scientists associated with the Action will be

encouraged to include a link to the website in their email signature files to promote the activities to colleagues. A webpage on Wikipedia (with links from Wikipedia pages on related topics) will be used to "funnel in" interested parties to view the Action website.

- *Publications and presentations.* Results arising from the collaborative work in the Action will be published in high impact journals and presented at national and international conferences (as soon as any intellectual property is protected by patents). All Action members will be obliged to acknowledge COST funding in peer reviewed papers and conference proceedings. Each Action member will include the COST logo and make reference to the Action in conference presentations and lectures delivered to industrial and university audiences.

- *Intellectual property (IP) strategy and patents.* The Action aims to provide opportunities for collaborative work but will not interfere at the IP stage other than to encourage participants to take the necessary steps to protect their inventions. Participants will follow the guidelines of their own host institutions for processing confidentiality agreements and patent applications.

- *Evaluation and monitoring.* All respective instruments e.g. STSM, WGM, CGM, workshops, summer schools etc. have to be monitored and evaluated once they are finished. Written reports from all the actions respecting the COST procedures will contain scientific issues and also clear cost breakdown. All reports will be submitted via respective coordinators to the MC for evaluation and final approval, followed by publication on the web page.

- *Other public engagement.* The MC will actively encourage participants to engage with the general public, school pupils and undergraduate students whenever opportunities arise. Once new and exciting results have been published, press releases through local University press offices will be used to promote results of the Action to the media. Action members who are invited to participate in radio, TV or newspaper interviews will endeavour to highlight the activities of the Action and COST itself (including links to the website where appropriate). Action members will be encouraged to promote the

activities of the Action through examples/case studies in their undergraduate/postgraduate lectures.