TRANSLATION AWARD PRELIMINARY APPLICATION

This form must not be used for preliminary applications for Seeding Drug Discovery. Preliminary application forms for Seeding Drug Discovery are available at http://www.wellcome.ac.uk/stellent/groups/corporatesite/@technology_transfer/documents/web_document/wtx027222.doc **and must be completed in conjunction with the information for applicants available at** http://www.wellcome.ac.uk/stellent/groups/corporatesite/@technology_transfer/documents/web_document/wtx027225.doc

Applicants to the general translation fund are expected to first submit an Executive Summary as a preliminary application. Applicants for a Strategic Translation Award should first contact Technology Transfer before submitting any summary or preliminary application.

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1) Proposed project title

Customising generic software methods to differentiate between cell types.

2) Please provide a summary of the technology to be further developed (max 200 words).

Resolving minor differences between cells, especially normal to pathological, requires a trained eye.

"Machine vision" is inadequate because available systems are programmed to perform simple repetitive tasks while hardware cannot distinguish shapes, objects or patterns like the human eye.

Our "software vision" is different because it starts with the digital representation of the image. Proprietary "MetaMeasures" are derived and visualized as "profiles" that can be compared at a glance. Even more so, they can be analyzed by software so that selection criteria can serve as a basis for making decisions.

The result is that we will resolve parameters such as overall shape, nuclear/cytoplasmic organisation, minor staining differences and edge variation. The first capability is shape discrimination, the second is sub-compartmentalisation of the key parameters to provide a population description, the third is mapping back to which entities are of significance and which are normal variation. The testable end point will be the ability to match resolution of normal to abnormal cells to the capability of a trained operator.

Staging will go from resolving completely different cell types, to resolving obviously different cells of the same type, to minor cell differences. In this way the limits of the resolution capability, false negatives/false positives will be quantitated. The hypothesis is that resolution capability is greater than by current methods and by human microscopy.

3) Please give details of a) key points of validation, b) current stage of development of the technology and c) any other relevant background information.

Prof. Pankaj Vadgama of the Interdisciplinary Centre in Biomedical Materials will lead the research, with input from Prof. Lawrence Litt of the Center for Cerebrovascular Research at the University of California, San Francisco.

The software methods that can be applied to any complex data system, have been used with a variety of digital images from a number of imaging technologies. In that process, proprietary procedures for deriving "metadata" and "metameasures" have been developed. While these software principles have been established as a generic foundation, domain-specific applications need to be programmed to examine measuring results or images from specific contexts.

It is felt that the differentiation of cell types is one of the best possible applications to achieve progress for healthcare.

4) Please provide details of the proposal, using the box below and including the following (maximum of 4 pages):

(a) The plan of investigation proposed to be funded by the Trust including: the specific aims and objectives; at least 2 milestones, for the Trust-funded component during the course of the project (funding maybe dependent on achieving milestones); and how this proposal will ultimately lead to a healthcare benefit.

(b) A Gantt chart or similar graphical overview of the tasks to be undertaken, their sequence and duration for the entire project including those (marked separately) that will be undertaken in parallel but without Trust funding (if applicable) and key development steps after Trust funding. What other funds (if any) are contributing to related project tasks in the Gantt chart. Please give a brief description of the work to be undertaken with these alternative funds.

(c) How the project will be managed to deliver the milestones and key objectives, describing in-house expertise and any to be accessed externally.

a) Aims and Objectives

The project aims to provide a software system that allows users to differentiate cell types for the purpose of biological, medical and pharmaceutical research, diagnosis and monitoring therapeutic or other progress. For ease of use, the system is to become a "web service" that can be used by anybody with access to the web.

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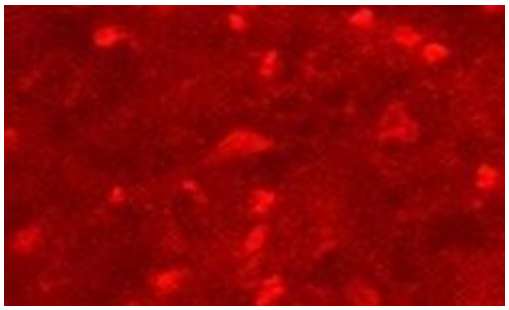
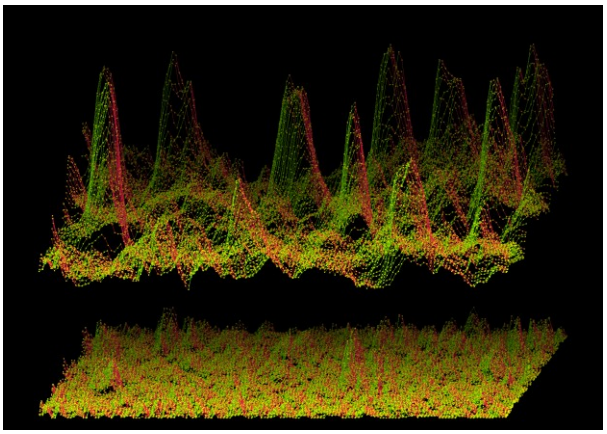
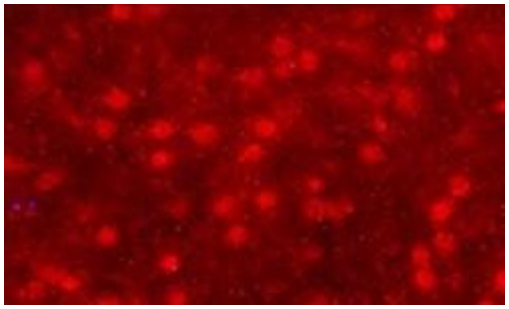
The objectives are to build an expert system that makes use of the insights of a mathematician inventor, knowledge management experts and software developers - for the benefit of microscopists, cytologists, biochemists, pathologists and scientists working on understanding phenomena at microscopic scales.

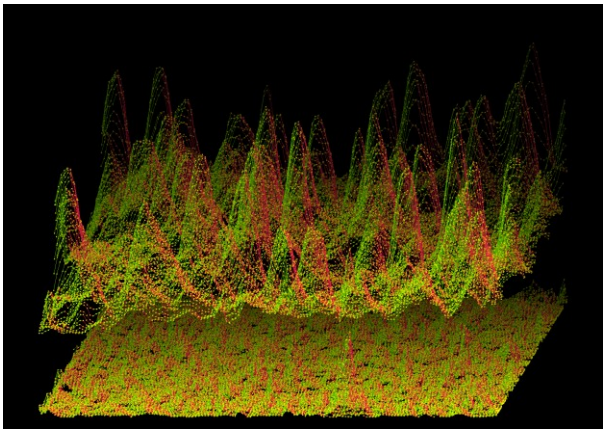
The core of the project is the development of a vocabulary for cytology. While we want to build on existing work, the vocabulary will also be able to receive input from users. Above all, its cytological terms will need to match the technical descriptors derived from a new approach to analysing digital images.

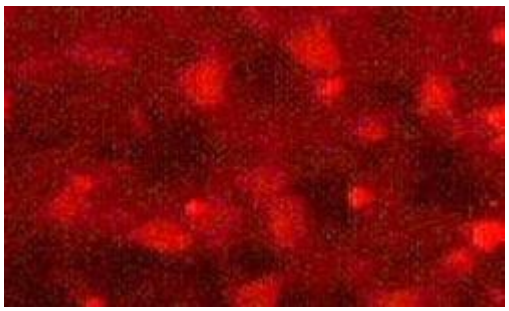
This new approach is demonstrated by the re-visualization of brain cells and comparing them during different phases of oxidative stress arising from intracellular production of superoxide.

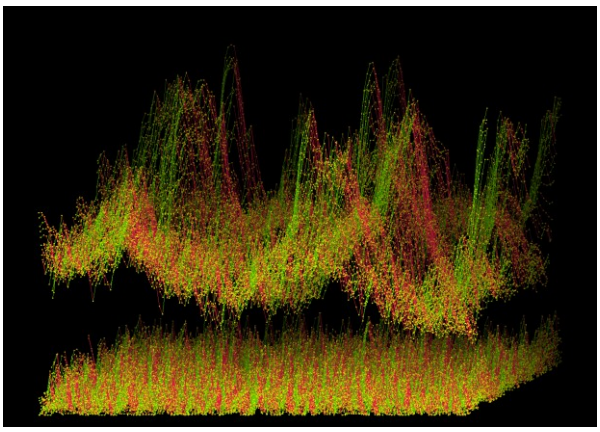










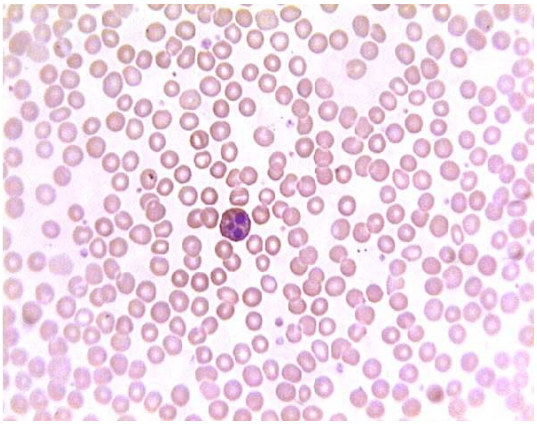


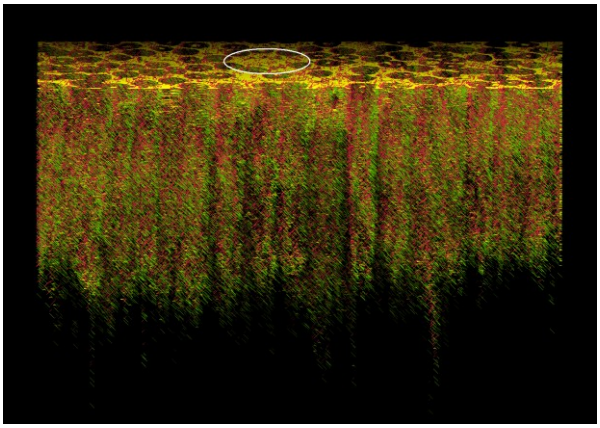
Treating an image as a high-dimensional matrix, our prototype software "slices" or "layers" its input for more detailed examination and more accurate representation of its components. For the human eye, a new visual depth is achieved and other visual effects can be realised. For the software, new quantifications can be derived.

By using "software vision" as our innovative technology, we propose to match our proprietary abstract descriptors with appropriate cytological terms. Furthermore, the biological, chemical and medical contexts will be taken into account.

Abstract image descriptors can be visualized as novel "image profiles". These can be compared visually at a glance. But the software will be able to compare thousands of such profiles automatically.

As another example, the one white blood cell among the surrounding red blood cells can be spotted on the surface of the re-visualization below. The quantified depths offer valuable information in addition to the new representation of red and white blood cells.





The research challenge consists in matching what "image profiles" represent with the expertise available in cell cytology so that new insights can lead to new conclusions and decisions.

The software challenge lies in conveying fundamental conceptual insights and translating generic methods into specific applications such that on-line services can be sustained financially.

The more the system can be fed with expertise about cell descriptors and their contexts, the better it can be trained to recognize and select images – first based on image profiles, later on image contents that can be described accurately and specifically, within the respective scale and context.

The project consists in three streams: one is to formalise the vocabulary to describe data bases of images. The other is to develop code that associates images with the vocabulary. The third stream integrates the feedback mechanism between user input and what is produced on screen. Instant on-line testability and usability is therefore key for the development on-time and on-budget.

The first steps are to research existing vocabularies and to build a data base of relevant microscopic images. Establishing procedures for integrating vocabularies so that they become a combination of menu options, user controls and drop-down lists is the task of the software team.

Subsequent steps make the data base of images searchable as part of prototyping a usable system. This is a bonus adding significant value to web-based science.

Milestone 1
To have a prototype as a skeleton for use is the first stage from the software point of view. From the cytological point of view, this means having a first vocabulary describing a data base of images to distinguish completely different cell types.

Milestone 2
Distinguishing minor cell differences is the goal for the second phase. It means fine tuning the interface between user input, the emerging vocabulary, the image processing code and the user output.

Milestone 3
Our innovative approach claims that the resolution of the imaging technology determines the quality of possible differentiations. Assessing statistical errors within these boundaries will allow us to measure the the system as a whole and to determine the areas that require further development.

b) Tasks undertaken

The tasks differ between the scientific team and the technological team. For the purpose of multi-lingual implementation, close collaboration with a German team is planned.

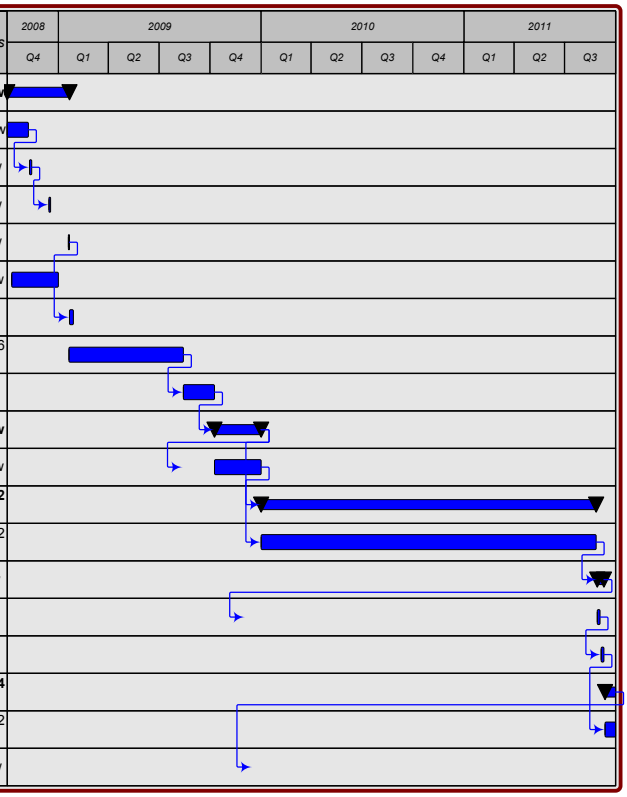
While the scientists supply all information required to build the planned system, the software team needs to ensure that what they are building is not only on target as far as functionality is concerned but also regarding the usability and user-friendliness of this new instrument of investigation.

The scientists will concentrate on image collections, vocabulary research, on-line usage and refinement (tasks 2, 3, 5 and 6).

The software team will concentrate on design, planning, multi-lingual implementation and eventually on-line marketing and PR (tasks 1, 4, 7 and 8).

Task 6, "on-line refinement" is the best expression of the on-going collaboration between the two teams. This collaboration is fundamentally ensured by on-line tools and processes. However, face-to-face meetings are even more necessary to avoid misunderstandings and mis-interpretations.

ID	Task Name	Resource Allocations	Start	Finish	Days
1	**Task 1: System Requirements**	**ABCD**	**01/10/2008**	**23/12/2008**	**12w**
2	Design Concept	ABCD	01/10/2008	07/11/2008	5.6w
3	Functional Specification	ABCD	10/11/2008	13/11/2008	.8w
4	User Specification	ABCD	15/12/2008	17/12/2008	.6w
5	Application architecture	ABCD	19/01/2009	20/01/2009	.4w
6	**Task 2: Image Collections**	HIJKL	09/10/2008	31/12/2008	12w
7	**Task 3: Vocabulary Research**	HIJKL	21/01/2009	27/01/2009	1w
8	**Task 4: On-line Prototype**	DEFG	20/01/2009	13/08/2009	29.6 w
9	Cell types	HIJ	14/08/2009	08/10/2009	8w
10	**Task 5: On-line Usage**	**DEFG**	**09/10/2009**	**31/12/2009**	**12w**
11	Minor cell differences	HIJ	09/10/2009	31/12/2009	12w
12	**Task 6: On-line Refinement**	**HIJKL**	**01/01/2010**	**26/08/2011**	**86.2 w**
13	Statistical assessments	ABHIJ	01/01/2010	26/08/2011	86.2 w
14	**Task 7: Multilingual Implementation**	**ABC**	**29/08/2011**	**09/09/2011**	**2w**
15	Familiarisation with German team	AKL	29/08/2011	02/09/2011	1w
16	German/English Vocabulary procedures	ABC	05/09/2011	09/09/2011	1w
17	**Task 8: On-line Marketing**	**ABJK**	**12/09/2011**	**07/05/2013**	**86.4 w**
18	Inviting Beta Testers / Potential Clients	ABJK	12/09/2011	06/05/2013	86.2 w
19	PR to Magazines	ABJK	07/05/2013	07/05/2013	.2w



c) Project Management
Both knowledge organization experts, Dr. Lilly Evans and Robert A. Bater, are experienced project managers equally capable of supervising the software development process while liaising with the scientific team.

In Berlin, Stefan Schridde teaches project management and has already initiated the voluntary work of a group of programmers.

5) Please provide details of the potential healthcare benefit of the technology

Differentiating between normal and pathological cells is of great benefit for any diagnostician.

Distinguishing between minor cell differences is of benefit for anybody watching illness deteriorating or progress through medication or other biological influences.

Assessing the system quantitatively will be the quality assurance for advancing the state of the art in cytology as the basis for biochemistry and other pharmaceutical applications.

6) COMMERCIAL MATTERS

(a) Patent information (continue on another sheet if necessary)

Application number:	
Priority date:	
Inventors:	
Applicant:	
Funding source:	
Title	

(b) How do these patent(s) or patent application(s) relate to the proposal?

(c) Describe any freedom to operate issues that have been identified or that might arise and how these will be or have been addressed. Include the type and date of any searches that have been conducted.

(d) **Describe any new types of intellectual property that can be anticipated including how the identification of these inventions will be managed.**

The IP behind the software methods is protected through 'black boxing' using the software MATLAB which offers 'toolboxes' for use by client software.

The IP resulting from the use of the software remains to be managed.

7) Please describe the competitive advantage of the proposed technology over current approaches

As far as we know, the only comparable research in terms of image analysis is carried out by Prof. Torralba at MIT, but it is limited to digital cameras without microscopes. The 3d metric approach is unique due to its genericness on a mathematical as well as metrological level. It can therefore be applied to all imaging technologies, and especially microscopes at nanoscale.
See
http://www.rdmag.com/ShowPR.aspx?PUBCODE=014&ACCT=1400000100&ISSUE=0805&RELTYPE=MIC&PRODCODE=0000000&PRODLETT=KC&CommonCount=0

Furthermore, the 3d metric approach is not only independent of the application domain but also of the imaging technology. While this is counterintuitive regarding scientific expertise, it offers a greater business potential.

8) Please describe why at the end of Trust funding the technology will be attractive for follow on investment or commercial exit and how this will be achieved

The ability to distinguish cell types serves as proof of the usefulness of the software. As it has a wide variety of possible other applications, any investor will want to participate once this usefulness can be demonstrated.

For example, other vocabularies can be developed through collaboration with other scientific teams for further exploiting the software IP.

9) Please identify parties that would be interested in such a technology and any approaches made to these to date.

Thomas Swan, a chemical company that produces nanotubes.
Johnson Matthey, a chemical company specialising in gold.
GlaxoSmithKline for controlling the quality of its pharmaceuticals.
NLP, the National Physical Laboratories, for establishing nanostandards.
IoN, Institute of Nanotechnology, Glasgow, for developing nanomedicine
Prof. Dr. Lawrence Litt, Department of Anesthesiology, University of California, San Francisco.

10) Please provide an approximate budget for the project

£1.6 million

11) If this is a resubmission of a project to the Translation Award scheme, please provide details of the key differences between that application and the current proposal.

The last submission was entitled “Multi-Scale Portals to Toxicity” thus addressing the challenge that had been proposed by the Chairman of the Government’s Task Force on Metrology, Characterization, Standardisation and Reference Materials who suggested that any innovation in metrology would have to address toxicity.

This project focuses on cytology and the recognition of image content. In close collaboration with an expert microscopist, differentiating between cell types from the grossest to the finest level is the challenge addressed by proposing to build a new instrument of investigation.

12) Please detail where you initially heard about the Translation Awards (pick one category)

MNT Network

Technology Transfer Member of Staff ☐ Presentation ☐ Advertisement ☐ Wellcome Trust website☐ Colleague ☐ other ☐