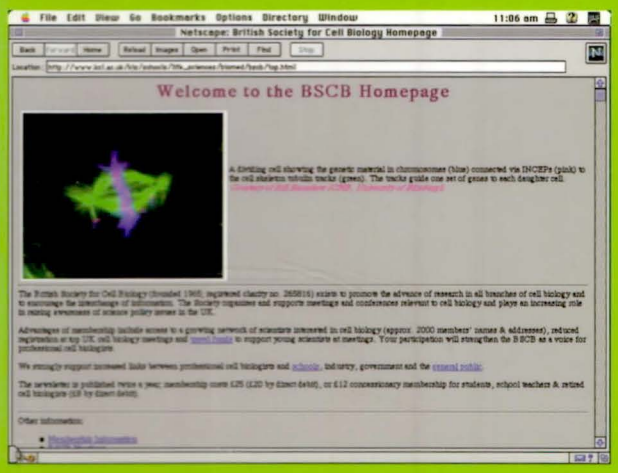
BSCB NEWSLETTER

Winter 1997



BSCB on the Web

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Monod

Abercrombie

Meetings future . . .

Joint BSCB/BSDB Spring Meeting 1998

BRITISH SOCIETY OF CELL BIOLOGY

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MEET THE COMMITTEE . . .
face to face!

BSCB Newsletter
Winter 1997

Editorial

A big thank you to all contributors of the newsletter and Committee over the past year, and to all sponsors of the BSCB. The highlight of this newsletter is the great deal on offer for members of the BSCB; free, or vastly reduced registration fees at the BSCB/BSDB joint meeting, next spring.

Also, we now officially have a BSCB website, thanks to the hard work of Simon Hughes and Paul Fraylich at the Randall Institute and free facilities provided by Kings College, London. Simon needs volunteers to help him with the website-as outlined in his article.

Moving to elsewhere in the newsletter you will see the benefits of joining the BSCB, as well as ways to contribute to the society. Speaking of which, I would like your photos; any picture, slide, or diagram, representing an event in cell biology is welcome. Please include a short figure legend (1–2 lines). The image will be displayed for everyone to see in a subsequent newsletter, so get yourself in the picture! To errant committee members: please provide me with a face to put alongside your name.

Lastly, any comments or suggestions concerning the BSCB or newsletter are more than welcome as letters to the editor.

The Editor

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NEWS

Vacancies on the Committee
Does the BSCB do what you want it to? If not, here is an easy solution — become involved yourself.

There are currently vacancies for two non-office bearing committee members. Please send suggested names for nominations, with full name, contact details (including e-mail address if possible), plus a supporting sentence, to the Secretary (Birgit Lane) by the end of March (or earlier). Self nominations are also welcome! Elections will take place at the next AGM, to be held during the meeting at Lancaster in April 1998.

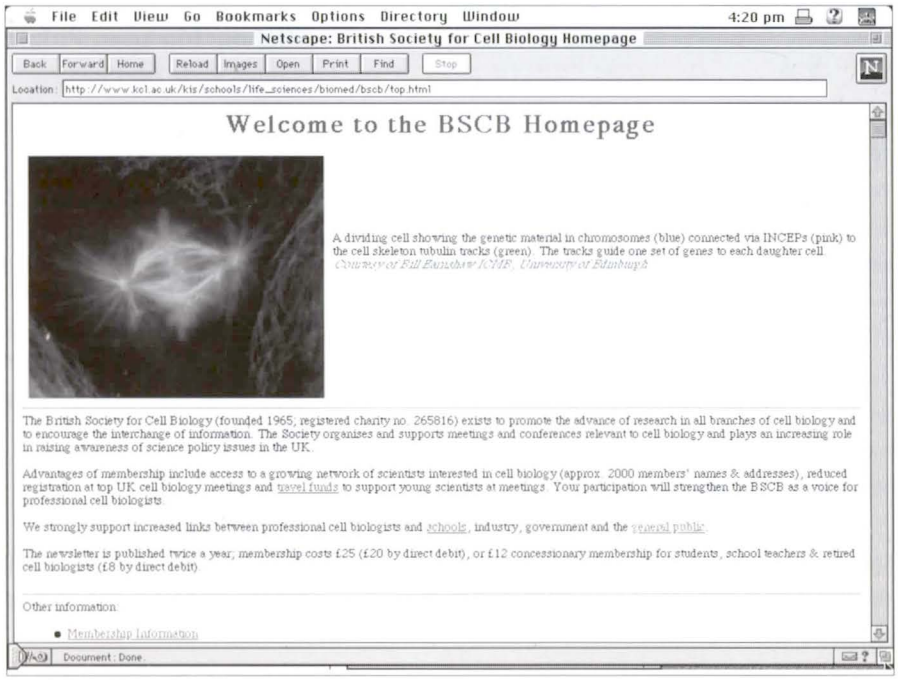
Call for Topics for Meetings
Are we missing something? If you think we are missing something from the programmes of the BSCB meetings, or would like to suggest a topic for either the annual meeting or for one of the smaller meetings, please let us know. All suggestions will be considered. Send your suggestions (plus your name, address and contact details) to the Meetings Secretary (Murray Stewart).

Science Education
Interacting with, and presenting research to science educators is fun and mutually rewarding. Contribute to science education, and give a BSCB supported lecture at the Association for Science Education's Annual Meeting. The ASE is the umbrella organization for science teachers in secondary schools. In January each year, the ASE is keen to hear about research in cell biology that is likely to have either a major impact on biology in general or challenges current thinking. Previous lecture topics have been programmed cell death (Martin Raff, 1996) and the human genome project (Kay Davies, 1997). Paul Nurse will talk about the cell cycle at the 1998 ASE meeting. If you are interested in presenting your research topic at the 1999 ASE meeting, please contact the BSCB secretary (Birgit Lane). Nominations are also welcome. Please provide name, address and contact details.

BSCB and the WWW

S Hughes, Kings College London

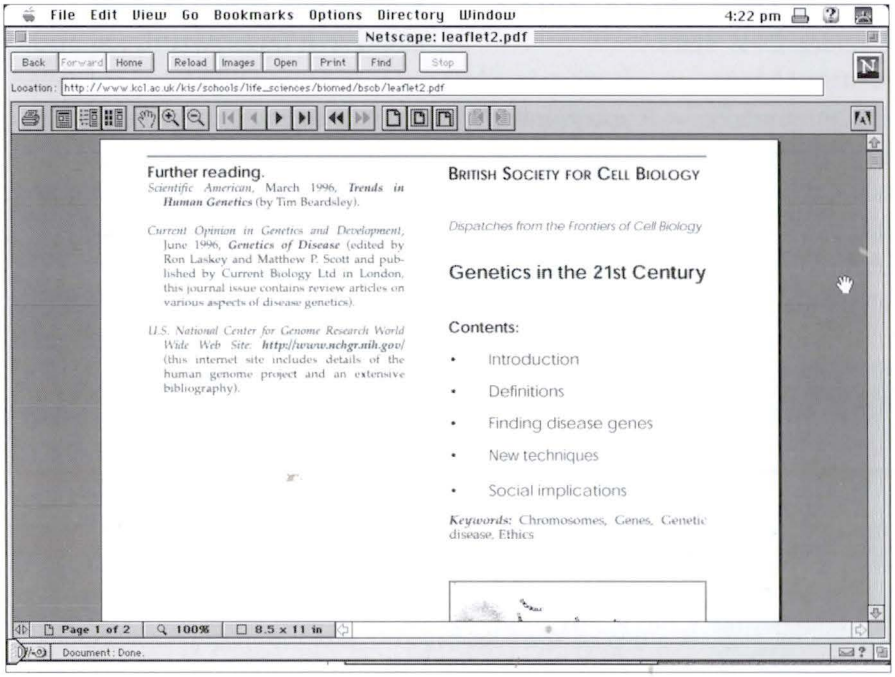
The BSCB has set up its own web site at **http://www.kcl.ac.uk/links/bscb.html**. The web, in general, has a dual role:



information provision combined with an element of 'marketing'. This is certainly true of the BSCB site. We hope our members and others will use the site to learn about the BSCB and its activities. There is a section, which we hope to expand, to explain cell biology to the broader public. There may also be a role for the site in raising our profile internationally, recruiting members and disseminating the views of the society.

Origin of the site
The BSCB committee decided in 1996 that a website is an essential adjunct of current professional communication. King's College London kindly agreed to host the BSCB site. A formal system to control the content of the site has

been set up. A small sub-committee consisting of Theo Bloom, Louise Cramer and myself vet the content of the site to ensure it does not infringe copyrights or propagate views unrepresentative of the BSCB as a whole.



Serving the BSCB membership

At the site you can find information on a variety of topics of interest to cell biologists. Probably the most useful pages are those with up-to-date information on meetings organised under our auspices. It is planned that the site will give basic information such as dates, location and subject matter. There will then be links to pages elsewhere that are maintained by local meeting organisers giving details of the schedule, registration etc. There is information about the Dame Honor Fell travel grant scheme for young scientists.

BSCB members will find the site useful for membership forms and information on direct debit payment. Other information includes how to contact BSCB officers, copies of back issues of BSCB Newsletters and information on how to participate in communicating our subject to schools and the general public.

As well as the prosaic, we hope to cater to aesthetics. Currently, there is a small gallery of images from cell biology. If you would like your (un-copyrighted) images to be put on display, feel free to email us your suggestion with a caption for the lay viewer.

BSCB and the wider community

With the continuing infiltration of cell biology into other areas of science, medicine and technology, many non-members wanting information on cell biology are visiting our site. With this in mind, and because the BSCB already has substantial links with schools, industry and government, we include in the site a very general description of cell biology and its importance within modern biology. We also highlight ways in which BSCB and its members are helping to explain scientific work and advances to the broader public. The committee considers this to be a valuable function of BSCB and is always eager to receive suggestions of ways the Society could support such endeavours.

BSCB is also keen to facilitate communication between cell biology and other scientific disciplines. To this end we include links to the websites of related organisations, such as the ASCB and BSDB. Suggestions for further links should be sent to Paul Fraylich (pef@helios.rai.kcl.ac.uk).

How you can help

The site is still in the process of development. So if there is something you think would be useful that is not there, please let us know. A function of the site that has not yet been fully developed is to give people in schools or colleges a starting point to gain an understanding of cell biology and its career opportunities. We think that this area has not been taken far enough and we would like to hear from members of the society or others who have suggestions on how we could improve the site. We are especially looking for volunteers to design and create pages, add links, graphics and so on. Offers of help would be greatly appreciated and should be sent to s.hughes@kcl.ac.uk.

Awards

Six bursaries available for young scientists

from Bulgaria, Commonwealth of Independent States, Czech Republic, Slovakia, Estonia, Hungary, Latvia, Lithuania, Poland, Romania and the former states of Yugoslavia

to attend

The BSCB/BSDB Joint Spring Meeting at Lancaster, 31 March to 3 April 1998.

These bursaries, sponsored by the BSCB and the Journal of Cell Science, will cover the cost of registration, accommodation and meals, and in 1997 a travel award of up to £250 per person. Applications, in duplicate, including a brief CV and concise reasons for wishing to attend should be sent to:

Birgit Lane, CRC Laboratories, Department of Anatomy and Physiology, Medical Sciences Institute, University of Dundee, Dundee DH1 4HN.

BSCB members — if you know of any young scientists from central and eastern Europe who would benefit from attending this meeting, please send them the above information.

Young Cell Biologist of the Year Poster Prize 1998

All research students are invited to enter the next poster competition at our Spring 1998 meeting at the University of Lancaster, 31 March to 3 April 1998. The prize is a trip to the USA to attend the 1998 ASCB meeting, to be held in San Francisco, December 12–16 1998, as their guest, with an opportunity to present the winning poster. For more details, see page 25.

Honor Fell travel awards

Honor Fell Travel Awards are made, up to a limit of £250, to provide financial support for young BSCB members to attend meetings. Applications are considered for any meetings relevant to cell biology, although the applicant must be presenting a poster or talk. For more details, see page 26

BECOME A MEMBER OF THE BSCB – TELL YOUR COLLEAGUES THE BENEFITS of MEMBERSHIP

Reduced subscription rates for some journals

Sponsorship of one day meetings

Up to £250 for travel to meetings (Honor Fell)

Travel bursaries (also available to non-members)

Prize for best poster at the BSCB annual meeting (Young Cell Biologist of the year).

Make the society work for you:

Write an article for the newsletter
Suggest themes and speakers for meetings
Volunteer to help organize a meeting

New BSCB Members from April 1997

Banbury, D.N.
Bray, S.E.
Bromley, Dr. I.M.J.
Byrne, Dr. C.
Camp, V.L.
Charge, S.
Cuttle, G.
Da Silva, R.P.
Dupree, Dr. P.
Fisher, R.J.
Hall, Dr. Anita
Hardman, M.J.
Harris, Brett S.
Hassan, P.
Hawley, Dr. S.
Haynes, L.
Heath, C.
Hutchison, Dr. C.J.
Jones, Dr. P.F.
Kirchem, A.
Lang, Dr. P.
Legg, J.
Leir, S-H.
Lewis, C.
Lewis, H.C.
Lowell, S.
Lu, Dr. X.
McCrossan, M-C.
McNeill, Helen
Meesaq, Anjela
Murphy, C.
O'Doherty, A.
Peake, M.
Salinas, Dr. P.C.
Slater, Dr. C.R.
Tzima, E.
Uziyel, Y.S.
Watson, J.A.

The Patenting of the *BRCA2* Gene

Few issues in biological research have produced as much concern and debate as the patenting of human genes. Recently, the patenting of the discoveries of the two genes associated with hereditary breast cancer, BRCA1 and BRCA2, have produced public action groups, government committees, and numerous articles in scientific and not so scientific journals. It seems many scientists have strong opinions and most are opposed to such patenting – fearing it could jeopardise research or render such discoveries into the control of 'commercial entities solely seeking profit'.

As one who is intimately involved in the patenting of such genes, and led the patenting of the BRCA2 gene, I hope to shed some light on the reasons why I believe patenting is important and, in most cases, is beneficial in transferring new discoveries into the healthcare system for the ultimate good of the patient.

The Discovery of the *BRCA2* Gene

First, a little background. Breast cancer is the second most prevalent cancer in Western societies, being surpassed only by lung cancer. Approximately 10% of all breast cancer cases can be ascribed to a hereditary association. This is particularly true of early breast cancer cases where the age of the sufferer can be as young as 18. Of this 10%, roughly half is due to a mutation in the *BRCA1* gene, while around another third is due to mutations in the *BRCA2* gene (1,2, 3).

In 1994, BRCA1 was discovered by a group from the University of Utah in association with Myriad Genetics, the Salt Lake City genomics company (4). There was initial disquiet at the patenting of such an exciting genetic discovery. It was also evident at this time that a second gene was playing a critical role in causing hereditary breast cancer and a race was initiated to find this gene (3). This race was given added 'spice' by the fear that, if Myriad were first to discover and hence patent this gene, they would have a dominant position in testing for both BRCA genes. Researchers involved in this race quickly fell into two camps, those supported by Myriad and those members of a consortium led by Dr Mike Stratton at the Institute of Cancer Research, Sutton, Surrey.

How do *BRCA* genes cause cancer?
BRCA1 and *BRCA2* are cancer-susceptibility genes; mutation of either gene predisposes a person to breast cancer. Like other cancer-susceptibility genes, there are thought to be two pathways to the onset of cancer (Kinzler and Vogelstein 1997, *Nature* 386, 761–763). The 'gateway' pathway is initiated by mutations in both alleles of a gateway gene (a gene that directly regulates cell growth or cell death). The 'caretaker' pathway is initiated by mutations in both alleles of a caretaker gene (a gene that maintains genetic stability). This pathway leads to cancer if the subsequent genetic instability that occurs causes a mutation in a gateway gene. Current known properties of *BRCA* genes are consistent with them being either gateway or caretaker genes.

Most researchers in the field believed it was only a matter of time before the superior funds of the genomic company would allow this group to announce the discovery of this second breast cancer gene. But against the odds, the group of researchers led by Mike Stratton and including Dr Alan Ashworth, Dr Richard Wooster at the Institute of Cancer Research and Dr Andy Futreal at Duke University, North Carolina, stunned the research community by announcing that they, and not the Myriad consortium, had discovered the *BRCA2* gene. This 'victory' for Mike's team was, for me and the company I work for, just the beginning of a difficult but exciting challenge.

Filing the Patent Application on the *BRCA2* Gene

Even before *BRCA2* was fully identified, the discovery of the first mutation which corresponded to the incidence of breast cancer in a large Irish family, produced much excitement in Mike Stratton's group. This also presented a difficult conundrum. The group had opposed the patenting of genes, and had specifically not joined the Myriad consortium because of disagreements with the way the company was proposing to use the *BRCA1* discovery. Nonetheless the importance of such a finding and the realisation that such a discovery could have a profound effect on the way susceptibility to breast cancer is tested meant that a carefully considered, but extremely rapid, consultation was needed with many interested parties. Thus, Mike Stratton immediately discussed the implications of the discovery with lawyers and directors at the Institute of Cancer Research and the charity which funded the research, the Cancer Research Campaign (CRC).

The organisation which is responsible for filing patent applications on behalf of CRC and licensing those patents to commercial companies is the subsidiary, CRC Technology (CRCT). This is a wholly-owned company which is, in effect, the commercial arm of the CRC's research portfolio. Thus, CRCT were consulted as to the appropriate course of action at the exciting point of the research after the identification of the first mutation.

After discussions with numerous interested parties, all in the space of a couple of days with telephones buzzing, it was decided it would be prudent to file our own patent application. Why? This was a very difficult step to take for many scientists, particularly for the group just about to sequence the *BRCA2* gene. Despite the many concerns addressed, CRCT had to take a pragmatic approach and deal with immediate concerns. We were not going to alter patent law overnight and it was important to obtain our position on this critical discovery before any other party. This would allow us the luxury of discussing and consulting with all interested parties concerning the best way to exploit this discovery for the benefit of the cancer patient – afterall, this is the ultimate aim of research, something that often gets overlooked! The only effective method to obtain a legal position on this discovery, and to prevent other less alturistic organisations obtaining a position, was to file and support our own patent application as soon as possible.

Our first concern was the speed of the public announcement of the genetic sequence. This concern was compounded by the fact that the Sanger Centre in Cambridge were sequencing the *BRCA2* interval, containing the gene, and were to publish this interval sequence. Any such public 'disclosure' could seriously damage the potential of obtaining a strong patent. Fortunately, Mike Stratton's group had begun sequencing the *BRCA2* gene before this announcement and the filing of our first patent application was rushed through just ahead of the Sanger Centre announcement. As Mike's team sequenced more of the gene, a second application was filed.

The next event was the publication of the discovery in *Nature* and the attendent press conference and resulting newspaper articles. Thus, the paper was sent for rapid review to *Nature*. On December 22nd, 1995, the day before the paper was due to be published in *Nature*, a press conference was organised announcing the discovery of the *BRCA2* gene. Additionally, the filing of our patent application was announced. Our first fears of competing commercial activity, and validation of our reason to file a patent application, came later that same day. Myriad announced to the US press that they had discovered the *BRCA2* gene and had filed their own patent application. Thus, there appeared to be two competing patent applications covering the same gene.

What's a Patent for?

It is important at this stage in the story to understand what a patent is and what it is for, an area of much misunderstanding in my experience.

The owner of a granted patent has only one right, that is to stop others from exploiting his/her

invention. There is no obligation to actually practice the invention. Of course, in reality, noone would go through the difficult, long, and very expensive procedure of actually obtaining a granted patent if they were not going to make some use of it. This also means that the patent holder does not have to profit from the invention or keep exclusive rights to it.

For a discovery to be patentable, it must be novel (unknown to the public), inventive (often the most difficult concept, because what is inventive today, quickly becomes obvious in the fast moving world of modern science; for example, recombinant protein technology was extremely inventive when the patent was filed in 1976), and useful (again a somewhat difficult concept, but the 'discovery' must have some sort of industrial use).

Turning to the patenting of genes; genes have been patented for many years, indeed thousands of patents have been granted by patent courts all over the world. Genes can be considered to be novel, inventive and useful. A gene is a sequence of nucleic acids, just like a protein is a sequence of amino acids, or complex carbohydrates are sequences of sugars. All these sequences are 'compounds', albeit very complicated compounds, and all are treated the same under patent law. New, previously unknown, genetic sequences are novel, clearly because they are new and noone could previously know of the sequence.

As to inventiveness, it can be argued that the finding of a particular gene is merely an awful lot of hard work and luck, but I would submit that, at least in this point in time, a considerable amount of skill is still involved, finding genes linked to diseases is not yet routine! Finally, with industrial usefulness there is some concern that finding a gene *per se* is not actually an 'invention' because it has no real use. Well that is true, but the use of genes linked to specific diseases is clearly useful in the diagnosis of such diseases. In other words, the use of a novel and inventive discovery doesn't itself have to be novel and inventive. Often the industrial use is quite obvious.

Thus, by the strict interpretation of patent law, genes are and always have been patentable and will remain so – as the recent directive of the European parliament has clearly stated. But what does this mean to the rest of us, if an organisation 'owns' the patent on a particular gene? In the simplest terms, the owner of a granted patent (it takes many years to actually get a patent granted) has the exclusive right to practice the 'invention' or to license that right to anyone else. It is important to realise that, in the case of a patent on a gene, the 'invention' is really the industrial use of the gene, not the actual gene *per se*. Noone will ever 'own' anyone elses genes, they are obviously a persons own property. It is the industrial use of the genetic information encoded by a gene that is really the basis of a patent.

There are some difference in US and European patent law, but most are relatively minor for the purposes of this article. The one difference of note is that the US has a concept of 'first to invent' while the rest of the world use a 'first to file' system. Thus in the US, you can be second to file, but if you demonstrate that you actually made the invention first, you can receive a patent. The US, since 1996, now allows such evidence of first to invent to be derived from research undertaken in other countries, hence the recent emphasis on notebooks, countersignatures and so on.

Another important concept in the UK that is often overlooked is the difference between inventorship and ownership. A scientist which makes an intellectual contribution to the invention, such as the finding of a gene linked to a disease, is an inventor but rarely, in the UK, is the owner of the invention. The owner is usually the employer of the scientist, in most cases the host University. It sometimes comes as a shock to scientists that they do not own their invention and indeed often have no legal rights to the decision whether to and when to file a patent application covering their work. Of course in reality, it would be impossible to file a patent application without a lot of help from the scientist and one of my major roles is to explain why, what, and how a patent can be filed to assist in the development of a particular technology,

while still allowing publication. Additionally, most University contracts of employment have a provision for sharing any revenue generated by the patent with the inventors named on the patent.

After the Filing of the BRCA2 Application

The decision whether to file a patent application covering the *BRCA2* discovery was a joint decision between the scientists involved, the host institution, in this case the Institute of Cancer Research, and CRC Technology. Although patenting genes in nothing new, within patent law, there are still many issues of ethical and moral concern which are extremely important and do need careful consideration and consultation. Just because a discovery is patentable does not mean that one should file a patent application. Our main fear, which turned out to be wholly justified, was that, by not filing, we would allow the initiative to be gained by another party which may not have the same ideals as the scientists, the Institute of Cancer Research and the Cancer Research Campaign. By filing an application, we were effectively saying that we want to be in the best position to decide how to use this discovery to obtain maximum benefit for the cancer patient.

Genetic Tests

In the UK, any company or organization offering genetic tests for BRCA mutations are expected to comply with a set of voluntary guidelines. Guidelines for genetic testing in general have recently been drawn up by the Department of Health's Advisory Committee on Genetic Testing. The guidelines include commitments to quality, confidentiality and conselling of patients/customers.

Thus, early in 1996, after the chaos surrounding the discovery, press attention, patent filing, and so on had died away, a group of experts from the Institute, CRC and Mike Stratton's team sat down to decide how best to use our patent position. The filing of a competing application by Myriad meant that we needed to make sure our patent prosecution was given the best opportunity to succeed, particularly in the US where such a patent prosecution procedure can be long and costly. Equally, all parties to this discussion were adamant that as wide a distribution as possible was provided for, and that any such diagnostic service using the *BRCA2* gene should be undertaken using the highest ethical standards. Given these guidelines, and the support of the Institute and CRC, CRC Technology's task was to devise and undertake a licensing strategy that sought to defend our patent position while seeking the widespread distribution of the *BRCA2* genetic test, and under the highest standards.

A year and a half later, in July, 1997, we were to finally announce an agreement with the US diagnostics company, OncorMed, which satisfied all of these goals.

Thus, by filing our patent application we have been able to have a major say in the way the discovery is exploited for the benefit of the cancer patient. For example, because of the CRCT position, if the National Health Service, UK, chose to offer a diagnostic test for *BRCA2*, they will be granted a free license. The next stage is to prosecute the application in various countries to obtain an actual grant of patent, but that is a long, and ongoing story which will not see a final conclusion for many, many years.

Dr. Guy Heathers, Head of Business Development, Cancer Research Campaign Technology.

References

1. Hall JM, Lee MK, Newman B, *et al*: Linkage of early-onset familial breast cancer to chromosome 17q21. *Science* 250:1684–1689, 1990.

2. Easton DF, Bishop DT, Ford D, *et al*: Genetic linkage analysis in familial breast and ovarian cancer. Results from 214 families. *Am J Hum Genet.* 52: 678–701, 1993.

3. Wooster R, Neuhausen SL, Mangion J, *et al*: Localization of a breast cancer susceptibility gene, BRCA2, to chromosome 13q12-13. *Science* 265: 2088–2090, 1994.

4. Miki Y, Swensen J, Shattuck-Eidens D, *et al*: A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. *Science* 266: 66–71, 1994.

5. Wooster R, Bignell G, Lancaster J, Swift S, *et al*: Identification of the breast cancer susceptibility gene *BRCA2*. *Nature* 378: 789–792, 1995.

Riches: Mirages, Pitfalls and the Pot of Gold

Say you have discovered something in your lab with commercial applications. If you are wondering what the next steps might be, read on. Presumably you have sorted out ownership issues (you can review your employment contract and terms of supporting granting agencies, and talk to your university's technology transfer officer) and have filed a patent application.

You have a first meeting with investors. What can you expect of them? What do they want from you? How can you best prepare yourself? Here's an aerial view of the topography ahead, as you navigate unfamiliar terrain to the pot of gold.

The First Mirage

Venture investors put money at risk — venture investment is not a promise to repay, and is not secured by a mortgage on your house. If your discovery could be a new drug, the US Pharmaceutical Association estimates that chances are less than 1% that your discovery will make it to the marketplace and make money. Since it costs an average of $225 million (including failures) to develop novel pharmaceuticals, few venture investors have the capital or appetite for risk to support drug development. Rather, venture investors prefer to invest in 'technology platforms', where one basic concept underlies multiple products — ideally, products with large, growing markets and fat margins. For roughly the same amount of early-stage capital put at risk, the potential reward is greater. Due to the quirky nature of discovery, only about 3% of all university discoveries are suitable for venture investment in companies. The remainder is better suited for licensing out to companies who seek to bolster their own product pipeline by in-licensing.

The first mirage is that your discovery is probably unsuitable for venture investment as a start-up company. But if it is, the second mirage is that you must share your equity with a cadre of professionals, as well as with your venture investors.

The Second Mirage

It takes an experienced team (where experience means failing graciously and learning from failures) to run a company and to bring a product to market. The Silicon Valley venture investor of the 1970s and 1980s typically took a hands-on approach, meaning that an investor would write the business plan, serve as 'start-up CEO' on a part-time basis until things got going, and be closely involved with day-to-day struggles and decisions. Unlike their American counterparts, however, most UK/European venture investors have never run a company and don't want to. Their role is largely limited to banker, monitoring spending and raising successive rounds of finance until cashing out in an acquisition or initial public offering (IPO).

But your expertise is science, not business. It falls to you to identify a CEO who will recruit a suitably qualified team. You and the team should prepare the strategic analysis and write the business plan. The second mirage is the value of your contribution. In reality, your contribution diminishes as the value of the product increases, enhanced by the efforts of your colleagues.

The First Pitfall

This means that success depends less on the availability of capital, than on the quality of your team. Seek out individuals with a reputation for fairness and integrity. Begin your search early. Take time to evaluate your potential partners and the depth of their commitment to your vision. Working with good people is probably the most important guarantor of success in a landscape filled with quicksand.

The Second Pitfall

In vivo data is worth roughly five times more than *in vitro* data at the negotiating table. Sound *in vitro* data becomes commercially irrelevant if *in vivo* studies suggest there are serious issues with drug delivery and bioavailability. Also, having *in vivo* data can improve your founding equity position (or, under the licensing scenario, improve the terms for cash paid at milestones and royalty rates). Design an experimental plan with adequate controls that incorporates *in vivo* studies (preferably using models familiar to regulatory authorities). Have your results confirmed independently by other investigators.

The second pitfall is the paucity of funding support that is available to strengthen your initial dataset. For a new drug candidate, for example, you could conduct simple experiments that suggest formal preclinical studies. These studies concern: reproducibility and stability of the material (do you get the same chemistry with each batch, does it degrade on the shelf or in the fridge?); accumulation and clearance in tissues; and cytotoxicity.

The Pot of Gold

Hopefully the company prospers. As it does, it consumes more capital and your founding equity position is diluted. Venture investors expect that only 10% of their portfolios succeed. Venture investors look for a return on investment (ROI) of at least 20%. 'Success' is a function of amount of capital invested, increase in share price, and time period when money is working. Assuming you bought your founding stock at a penny per share, what can you expect as 'success'? Say you still own 1% of the company when it debuts on the stock exchange six years after founding. On average this would be 200,000 shares. If your shares are worth $10 per share, with only a 10% probability of success, the net present value of your founding stock is only US$125,000.

Or, consider the scenario where your discovery is licensed out, say your drug makes it to market after seven years, and earns US$50 million per year. With royalties of 5%, calculated on 10% net revenues, the net present value of your share (assuming you are one of five co-inventors) is about US$16,000 per year.

Venture investors focus on the variables that affect the ROI of their investment — the amount of capital risked, number of product development outcomes, probability of success, and time horizon until money invested is returned. No one promised that your pot of gold would be large.

Constance McKee is President & CEO of Xavos Corporation, a neuroscience company in California. She can be reached at chinarock@aol.com.

Conference Jacques Monod: Actin, Cell Motility and Signalling

Aussois, France 23-27th June 1997

This meeting was held in the CNRS Centre in the picturesque alpine village of Aussois, nestled on the edge of the beautiful and spectacular Parc National de la Vanoise. Despite being the height of summer, early arrivals to the conference were surprised to awake to 4 inches of snow on the first morning; by afternoon, however, it had mostly melted and we were treated to unbroken summer sunshine for the rest of the week.

The conference, organised by **Vic Small** and **Marie-France Carlier**, covered all aspects of actin structure, regulation, signalling and cell motility. Rather than list brief details of the more than 60 talks presented and in the interests of space, I have selected a few talks that personally interested me, and talks in areas where significant new advances have been made.

The conference began with the more structural and biophysical aspects of actin and associated proteins, and moved gradually through regulation and signalling to cell motility. A discussion of the actin filament structure by **Ken Holmes** was nicely followed by the beautiful cryo EM reconstructions of actin filaments presented by **Ueli Aebi**. He showed comparisons of F-actin polymerised in the presence or absence of phalloidin. Phalloidin, which is known to stabilise actin filaments, had little difference on the overall structure of the filament other than to increase the apparent density between actin-filaments suggesting that the sub-filaments were pulled closer together. Using phalloidin labelled with 9Å gold, he was able to show that the phalloidin-binding site most closely mapped to that proposed in the Kabsch/Holmes model of the actin filament.

Other work from **Peter Rubenstein**'s laboratory used genetic analysis of actin mutants in yeast and *in vitro* polymerisation assays to examine the importance of residues in the 'hydrophobic plug' proposed to stabilise sub-filament interactions in the actin filament model. Mutations in this region lead to temperature sensitive polymerisation defects probably due to reduced lateral but not longitudinal stability.

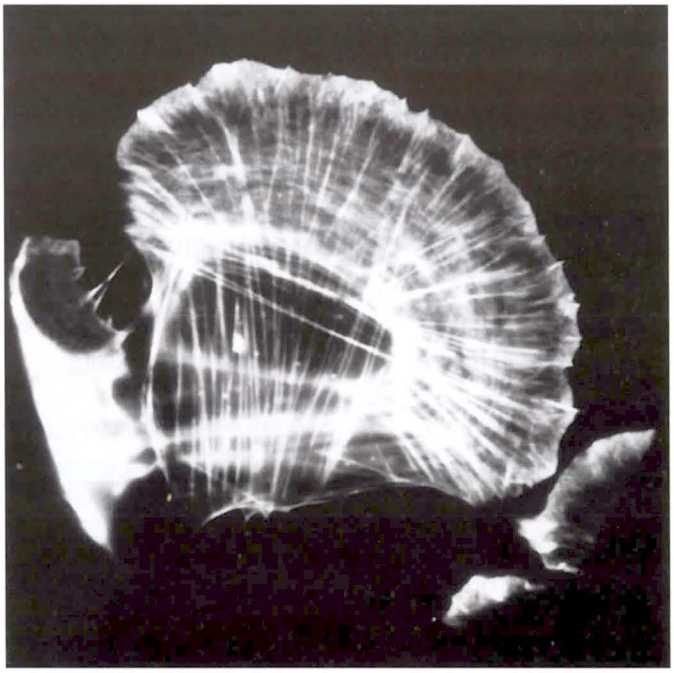
Using genetic analysis in *Drosophila*, **John Sparrow** described how mutations in actin affected actomyosin interactions. A single point mutation, E93K, in the secondary myosin binding site on actin, reduced velocity in *in vitro* motility assays and reduced force as measured with an optical trap, demonstrating the importance of ionic interactions between the interacting surfaces of actin and myosin.

A cell infected with *Listeria monocytogenes*. Each bacterium has a comet tail.

A short talk by **Fabien Gerbal** looked at the higher-order actin structures in the comet tails of *Listeria monocytogenes*. Using an optical trap, he was able to bend and flex the comet tail showing that it was quite flexible but at the same time maintained its structure. When broken, the tails depolymerised at the same rates from both broken surfaces, suggesting that, in this case, tails comprised many short filaments and not fewer

very long filaments. Several other talks addressed bacterial and viral motility in eukaryotic cells and cell extracts, with progress being made in understanding the mechanisms by which these organisms recruit the host's actin into generating comet tails.

Mike Way described how *Vaccinia* virus employs tyrosine phosphorylation to regulate tail assembly. Talks by **Juergen Wehland** and **Pascale Cossart** described the molecular analysis of the *Listeria monocytogenes* protein ActA, work which is beginning to unravel some of the complexities of this system which will be important for understanding actin polymerisation at the leading edge in motile cells. Complementing these presentations were talks from **Matthew Welch** and **Tom Pollard** describing the isolation and characterisation of the ARP2/3 complex from mammals and *Acanthamoeba* respectively.



Actin filament bundles and meshworks in a motile cell

Tom Pollard went on to propose how the concerted actions of ARP2/3 to polymerise actin at the leading edge, α-actinin at the lateral margins to stabilise actin filaments and actophorin to sever and speed depolymerisation of filaments in the rear of the cell were sufficient to account for cell movement seen in *Acanthamoeba*. **Allan Weeds** also argued for the need to increase the number of filament ends by ADF severing and capping filaments, thus accelerating pointed end depolymerisation as was suggested by Tom Pollard for *Acanthamoeba*. There followed some discussion and disagreement of the roles of ADF in actin dynamics.

Two presentations from **Dave Drubin**'s laboratory described the genetic dissection of cofilin structure and function in yeast – which nicely complemented the cryo EM reconstructions of cofilin decorated actin filaments shown by Allan Weeds. Another talk by **Patrick Hussey** described the cloning, biochemical analysis and cellular functions of plant ADF-like proteins and their involvement in pollen tube and root hair growth. Cell outgrowth in neurites was addressed by **Sohail Ahmed**, showing that the concerted actions of the small GTPases Rac and CDC42 drive neurite extension which is antagonised by RhoA leading to growth cone collapse.

Laura Machesky showed some quantitative analysis of the relative contribution of Rac, Rho and CDC42 to the F-actin content of Swiss 3T3 cells (beautifully correlated later by images of similar cells from Vic Small's laboratory), and went on to describe the role of Rho in the activation of Rho kinase and its effects in stress fibre contraction. **Keith Burridge** elegantly presented the same topic, but from the standpoint of Rho kinase and contraction mediated clustering of integrins and focal adhesion formation. Rho activation, of both Rho kinase and PIP kinase, has the combined effects (via separate pathways) of the formation and contraction of stress fibres, matrix rearrangements, membrane attachment and focal adhesion formation by

actomyosin-mediated integrin clustering. **Marc Bloc** also described the role of various kinases and phosphatases on integrin-mediated adhesion and cell spreading, demonstrating a role for calmodulin in controlling phosphorylation-dephosphorylation and activation of $\alpha 5\beta 1$ integrin via calcineurin and CaM kinase II.

Two excellent talks from **John Cooper** and **Velia Fowler** addressed more enduring problems concerning the regulation of sarcomere assembly. John Cooper described the functions of capping protein, a barbed end capper, in regulating actin dynamics and also proposed a model for the role of the related Cap Z and a-actinin in Z disk assembly. This was nicely complemented by Velia Fowler's presentation describing the role of tropomodulin, a pointed end capper, in establishing the framework for thin filament assembly in cardiac myocytes also in concert with Cap Z and α-actinin.

The final talks of the meeting described different aspects of cell motility. **Vic Small** described the organisation of actin filaments into orthogonal arrays in the lamellipodium and their progressive incorporation into microspikes and stress fibres as they progress back through the keratocyte cell. He also showed that as the keratocyte moves forward the cell body actually rolls along on top of the actively moving cell probably by an actomyosin based mechanism.

Daniel Choquet showed the rearward motion of large fibronectin coated beads on the upper surfaces of lamellipodia. Using optical tweezers he was able to stop the motion of the bead by detaching the integrins to which it was attached from the underlying cytoskeleton. This required surprisingly low forces, in the order of 5pN per integrin. This trapping also had no local effect on the cytoskeleton.

Traction forces were also addressed by the final speaker of the conference, **Yu-Li Wang**, when he showed details of an exciting new optically clear polyacrylamide-based deformable substrate. Using this substrate it was possible to look at the direct effects of locomoting cells on the substrate and to measure traction forces generated in different regions of the cell. Definitely a space to watch.

The organisers of the next Jacques Monod Conference on Actin in two years time, **Marie-France Carlier** and **Juergen Wehland**, will clearly have many developing and exciting fields from which to choose their programme: small GTPases, ARPs, the increasing amount of data from genetic analysis of actin and actin binding and regulatory proteins and novel approaches towards understanding cell adhesion and motility.

Steve Winder, Institute of Cell and Molecular Biology, University of Edinburgh

4th Abercrombie Meeting on Cell Behaviour: Control and Mechanism of Motility

St Catherine's College, Oxford, 28th September – 1st October 1997

Judging by the enthusiasm of the participants, lively debate, and number of comments received by the organising committee, the meeting was a great success. There were 4–5 talks in each category, a lively poster session and an excellent informal video session that happily over-ran its scheduled time.

The meeting was divided into topics:

- *Motile responses — the phenomena*
- *Intracellular control systems — transduction*
- *Cytoplasmic control of the motor machinery*
- *Cytoskeletal dynamics*
- *Dynamics of motility*

Motile responses — the phenomena

Gerhardt Gerisch gave an overview of motility and drew attention to the overlaps between this and endocytosis and cytokinesis, illustrating this by reference to *Dictyostelium* behaviour and the distribution of coronin at the leading edge of the cell, or at sites of phagocytosis (and exocytosis) and pinocytosis. He illustrated the redundancy in the four classes of cytoskeletal actin binding proteins. Myosin II knock-out cells can still undergo cytokinesis, but with a higher level of cortexillin at the cleavage furrow than wild types.

Adam Curtis showed the behaviour of cells confronted with various substratum geometries, and compared active cells (macrophages), which respond quickly, to 'lazy' cells such as chondrocytes, which are indifferent to surface patterns for many hours. Many cells seek edge discontinuities in their locomotion. Spatial 'awareness' of cells may be a function of membrane 'stretch' receptors, possibly chloride channels which are inhibitable by nitrate ions. Alignment of cells such as myocytes or tendon fibroblasts may be exploited in attempts at tissue reconstruction.

Robert Tranquillo showed a video of fibroblasts within a collagen gel repeatedly shunting to and fro along 'tracks', yet retaining the ability to contract the collagen (or fibrin). The cells could align radially along a directional RGD concentration gradient, or along pre-aligned collagen fibrils. Neurite extensions were longer along aligned collagen. The system is a dynamic equilibrium responding to internal and external forces: external compression of gels forces cells to align in the direction of the force.

Patrick Doherty reviewed neuron development and its requirement for extracellular signals. In particular, he discussed binding to N-cadherin and N-CAM or L1 which accelerate neurite outgrowth in a calcium influx-dependent manner that is not adhesion coupled. The FGF receptor is required for and integrates this response, and intracellular signalling downstream involves PLCγ and tyrosine phosphorylation.

M Mareel gave an overview of malignant invasion, emphasising the role of the cancer cells instructing local 'host' cells to facilitate the process by production of scatter factor/hepatocyte growth factor, adhesion molecules and lytic enzymes. E-cadherin block enhances invasion, reflected in 50% of such malignancies possessing mutations in this gene. In MDCK cells, the 'HAV' motif in cadherin molecules enables this process through intracellular coupling to the phosphorylation state of β-catenin. In colonic PC cells the invasive response to SF is reversed by several agents including platelet activating factor, IGF-1 and wortmannin.

Intracellular control systems — transduction

David Critchley described the focal adhesion complex and its integrin binding function, concentrating on the functions of talin and vinculin in

actin cytoskeletal organisation. Talin has 3 binding sites for vinculin and actin and may be a template for actin assembly, whereas vinculin is a coupling protein joining the other two. The assembly of stress fibres is dependent on active Rho transcripts. The Golgi protein Arf-1 is also involved by enhancing paxillin localisation to the focal adhesions.

Martin Humphries showed the roles of adhesion-dependent signals, both outside-in and vice versa. Allosteric cation binding (in particular Mn>Mg>>Ca) to the external domains of integrins allows binding regulation by conformational shape changes.

John Westwick reminded us of the roles of chemokines in motility control, with emphasis on leukocyte responses. The 35 or more chemokines are divisible into four broad families according to cysteine residues. These ligate to various receptors. Some have restricted localisations, such as the CXC receptor 2 – which is found on endothelial and smooth muscle cells, and regulates angiogenesis. The chemokines RANTES and MCP1 were shown to increase T-cell and monocyte migration using wortmannin-sensitive pathways. However, due to the multiple isoforms of PI-3 kinase, not all ligand effects are wortmannin-sensitive. Thus G-protein coupled effects in THP-1 cells were sensitive to pertussin toxin, but insensitive to wortmannin.

Patricia Salinas examined Wnt factors in axonal remodelling and synaptogenesis. Wnt3 is probably secreted by target cells and acts in a para- or autocrine manner. Wnt3 inhibits GSK3β enzyme activity and axon spreading through a lithium-sensitive pathway, and which also involves a fall in MAP1 phosphorylation that precedes changes to the cytoskeleton. Wnt7α induces a mossy fibre phenotype with concurrent rises of synapsin 1.

Cytoplasmic control of the motor machinery

Anne Ridley described the roles of the small G proteins Rac and Rho and their intracellular pathways in the control of cell motility. Rho has multiple targets, including focal adhesion kinase, paxillin and p130cas, and is active in actin dynamics by inducing its polymerisation, as well as regulating the phosphorylation of the myosin light chain via Rho kinase. In MDCK cells, Rho inhibits the scatter effect of SF/HGF without affecting stress fibres. In macrophages, the agonist CSF1 induces membrane ruffling and lamellipodia via a Rac-dependent pathway, while filopodia depend on cdc42 signalling. Macrophage chemotactic migration in a Dunn chamber is promoted by CSF1 in a Rac and Rho-dependent manner, but a dominant negative to cdc42 showed increased random migration only, a similar effect to that induced by TNFα. Since TNFα inhibits filopodia extension, it was suggested these structures incorporate gradient sensors.

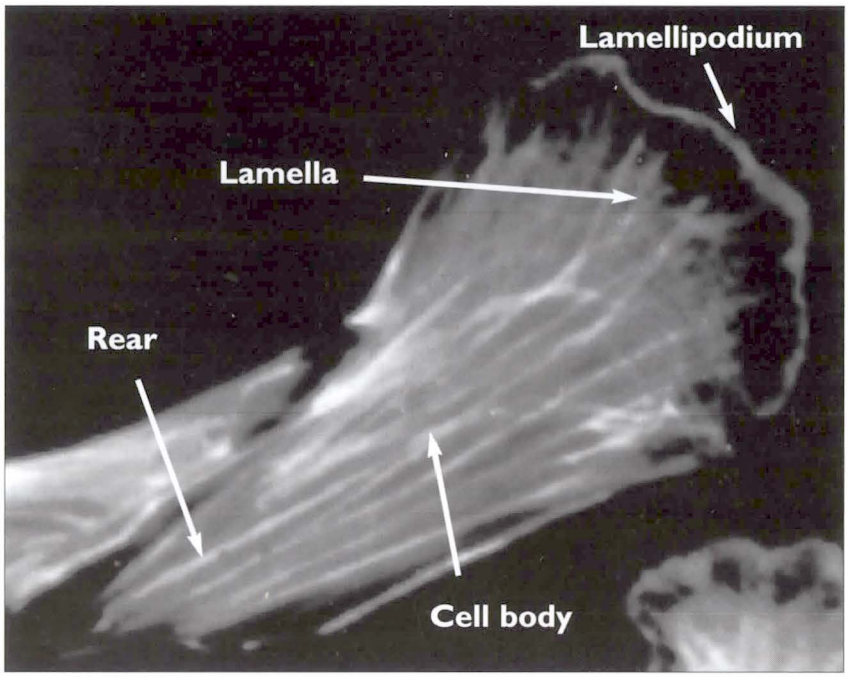
John Collard introduced Tiam1 as an inducer of Rac-dependent lamellipodia formation and invasivenes in T lymphoma cells. Tiam1 also raises binding of N115 neuronal cells to laminin, induces ruffles in 3T3 cells by a mechanism dependent on the amino-terminal domain of Rac, which also retains a tumourigenicity for the cells. In epithelial cells (MDCK), Tiam1 is associated with cell–cell E-cadherin junctions rather than free edges, and inhibits the effects of SF/HGF. The protein thus promotes T-cell adhesion to other cells, and hence enhances invasion, whereas it promotes cell–cell adhesion in MDCK cells and inhibits invasiveness.

Ken Howard reviewed the role of DrPAP2w in germ-cell guidance in *Drosophila* embryos. This factor is effectively a germ-cell repellant produced by the developing gut endoderm. The protein is a phosphatidic acid phosphatase, highly conserved across evolution. Its lipid substrate specificity is not yet known.

Alexander Bershadsky described the effects of microtubule disruption of 3T3 and MDCK cells on focal adhesion formation, which was dependent on the ECM molecule fibronectin. In transfection experiments using SV80 human fibroblasts, Rho induced large adhesions, whereas the smooth muscle protein caldesmon induced small ones, only the latter being insensitive to depolarization by KCl.

Cytoskeletal dynamics

Gary Borisy discussed the role of myosin II in cell body translocation, and compared the 'transport' and 'contraction' models. These cells have a more regular actin network than that of fibroblasts, which may help explain the 30-fold difference in migration speeds. Data on the ultrastructural organization of actin filaments in relationship to myosin, and myosin dynamics in live cells support dynamic contraction of the actin–myosin network to drive translocation of the cell body during keratocyte locomotion. The same mechanism may drive retrograde flow of myosin that occurs in stationary (but not locomoting), tethered keratocytes. The data are inconsistent with sarcomeric contraction.



Organisation of actin filaments in a locomotive fibroblast

Manfred Schliwa considered the role of centrosomes in determining cell direction. There is conflicting evidence. Some cells locomote happily without microtubules, and *Dictyostelium* pseudopod initiation precedes centrosome movement. On the other hand, aster formation is disrupted in cytochalasin-treated leukocytes, implying a role for intact actin filaments. Fibroblasts on glass (2-D) have centrosomes ahead of nuclei 75% of the time, while in collagen gels (3-D) this is only 50%. Wounded monolayers display edge cells with centromeres the 'wound' side of nuclei. The final importance of these observations remains to be seen.

Louise Cramer described actin structural organization and dynamics in locomoting fibroblasts. In the front and rear cell margin, the polarity of actin filament bundles and sheets is uniform, with barbed ends facing the margin. In contiguous bundles, in the middle of the cell (roughly mid-nucleus) polarity is mixed. Between these locations, polarity gradually changes from all barbed ends forward to all pointed ends forward. In marking experiments in live cells, in lamellipodia, uniform polarity actin filament organizations flow rearward. In lamellae, graded polarity actin filament bundles are stationary, and in the cell body there are forward moving and stationary dynamic actin populations. These data support a 'transport' model for translocation of the cell body during fibroblast locomotion. The data are inconsistent with sarcomeric contraction.

Mike Sheetz showed the use of laser trapping to follow membrane flow in cell movement. If large enough fibronectin-coated beads are placed on the upper surface of cells, integrin clustering is triggered and the beads move in a retrograde direction opposite to the advancing lamellipodium beneath. Using a silicon chip as a force transducer, it was clear that, in locomoting fibroblasts, traction force is oriented backward in front of the nucleus. Behind the nucleus, this is balanced by an equal, forward directed force. In the tail, traction force is 4-fold higher than in front of, or behind, the nucleus. Mike Sheetz concluded that these measurements are consistent with the organization of graded polarity actin bundles in the same cells, as described by Louise Cramer. In the front of the cell, the major

force is exerted via the cell body and lamella rather than the lamellipodia, corresponding to areas where myosin concentration is highest.

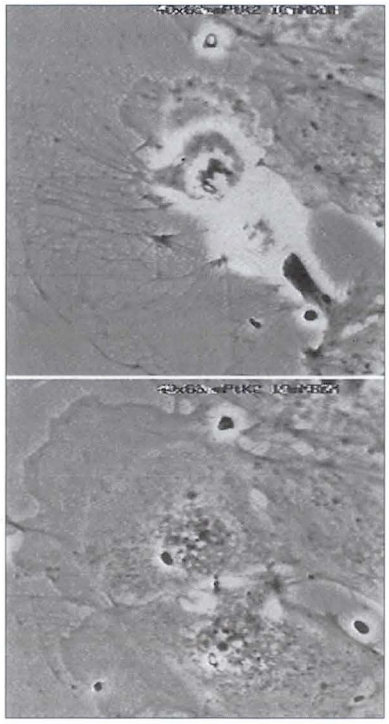
Dynamics of motility

Igor Weber used videos to show surface contacts of *Dictyostelium* and their rapid alterations with cAMP chemotaxis. Talin negative mutants had smaller areas of contact, but could divide. Coronin-negative cells had actin-rich pseudopods but devoid of other intracellular particles. Double coronin–cortexillin negative cells struggled far longer to divide, with 30% failing.

Tom Stossel used the ability of gelsolin to sever actin as a tool to study platelet spreading. Activation of the thrombin receptor induced F-actin assembly, shortly preceeded by a spike of intracellular Ca and a simultaneous fall in PIP_2 concentration. By chelation of calcium with EGTA and cytochalasin treatment, it was possible to prevent cold-induced (4°) activation of platelets, a clinically useful finding. Gelsolin negative cells (fibroblasts) could not ruffle nor become bipolar, while melanoma cells, negative for another actin binding protein, ABP280, were unable to locomote. ABP-polymorphs showed much membrane blebbing, indicative of an unstable actin network.

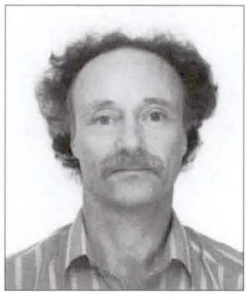
Michelle Peckham presented observations on myoblast locomotion. Using satellite cells as a myotube precursor, she showed that they express five myosins (I, II, V, IX and X), which had distinct intracellular distributions — for instance myosin I was lamellar, while II was not, and IX was around the central body only. Ectopic expression of β-cardiac myosin impaired cell locomotion, spreading and polarity. β-Actin over-expression produced flatter cells, while γ-actin led to spindle shaped cells.

Elliot Elson used *Dictyostelium* to study the forces which drive locomotion. Fluorescent beads placed onto the front margin of locomoting cells moved to the rear of the cell in a radial manner, becoming concentrated at the tail. A myosin II null strain still showed rearward bead movement, but this was slower, and the beads collected in a line, ie their motion was parallel. Myosin I and II double mutants exhibited rearward bead movement. In separate experiments using cell-contracted collagen rings, an important role for myosin light chain phosphorylation was found.



Top: cytokinesis. Bottom: respreading after cytokinesis.

Albert Harris presented the final talk and demonstrated a computer simulation of cell division in *Dictyostelium* myosin-null mutants. He also refreshed us with a video of sponges exhibiting motion. In terms of forces involved, tissue growth did not 'push', nor did adhesion 'pull', rather there was active motion. He challenged us to re-read the seminal works of Abercrombie to ensure we retained an overview of the problems of cell locomotion.



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BSCB/BSDB Joint Spring Meeting

Lancaster University, 31 March – 3 April 1998

General Information

Venue

The meeting will be held on the Lancaster University campus at Bailrigg, about 3 miles south of Lancaster city centre. The plenary lectures will take place in the Great Hall and the main BSDB/ BSCB symposia and the workshop sessions will be held in the Faraday lecture theatre complex. Tea and coffee will be served adjacent to the posters in the Nuffield Theatre and Minor Hall.

Accommodation

Accommodation will be in single rooms on the University campus. The registration form gives rates for dinner, bed and breakfast in either standard or *en suite* rooms. A small number of *en suite* twin rooms are available, charged at twice the single room rate. If you wish to book a twin room, contact the Lancaster University Conference Centre on the number shown on the registration form on page 23.

Programme

The BSDB and BSCB symposia will run in parallel. There will also be a parallel session on Skin and an evening workshop on GSK3. The scientific programme will begin at 9.00 promptly on Wednesday 1 April. Participants who plan to stay at Lancaster should arrive and register on the Tuesday evening. Others should aim to arrive by no later than 8.15 on the Wednesday morning in order to complete registration formalities before the scientific programme begins.

Registration Details

Pre-registration is essential and must be completed by 30 January 1998 to avoid a late registration penalty of £20. All registrants must complete the official form (attached), and must remit in full to cover all accommodation and meeting costs when submitting their form. Registrants will receive an acknowledgement and receipt, including details of how to arrive in Lancaster.

Meeting Charges

Members of the BSDB or BSCB can purchase an attractive all-inclusive package including accommodation, meals and registration for the entire meeting. For those who do not wish to attend the whole meeting, or who do not require the full accommodation and meals facilities offered, registration is payable which covers the costs of tea, coffee, abstract and programme booklet and social programme, plus the cost of conference organisation and hire of University facilities. Registrants choosing this option can purchase additional accommodation and meals as required but please note that all such requests must be made at the time of pre-registration, and cannot be arranged in Lancaster at the last moment.

Registrants who are not members of either society can either apply to join well in advance of the 30 January deadline, in order to take advantage of the Member Package, or else must pay the Non-member registration fee plus accommodation and meals as required. Note that there are discounted rates available for students. Details of how to pay are given at the foot of the registration form.

Social Programme

There will be private bar facilities with a late extension on the Wednesday and Thursday nights. A conference dinner will be held on the Thursday night followed by live jazz and a disco. The conference dinner is included in the Member Package, but others wishing to attend the conference dinner must indicate and pay for this when submitting their registration form. Those not attending the conference dinner may nevertheless come to the Jazz and disco evening.

Accompanying Persons

Accompanying persons must complete a separate registration form. All accommodation and meal costs must be paid at the time of pre-registration, although they are exempt from the registration fee. They may attend the social programme except for the conference dinner, unless purchased separately, but may not attend the scientific sessions, and will not receive an abstract/programme booklet.

Creche Facilities

Participants with children may be interested in using the University's Pre-School Centre on campus. The Centre caters for children aged between 3 months and 5 years old. Further details can be obtained by contacting the Centre directly: Tel: 01524 594464, e-mail: *m.kemp@ lancaster.ac.uk* or consult the Centre's web pages on *http://www.lancs.ac.uk/users/pre-school/*.

Car Parking

Participants travelling by car will be issued with parking permits on arrival. Please indicate on the registration form whether you require a parking permit.

Posters and Abstracts

There will be two poster sessions at the meeting. The first, on the Wednesday afternoon, is for posters related to the BSCB symposium on Cellular Localization. The second, on the Wednesday evening, is a general poster session for members of both societies. All participants are encouraged to present a poster at the meeting. Poster presentations from students who are members of the BSDB or BSCB, and who have not been awarded a higher degree at the time of registration for the meeting, will be eligible for the special poster awards. To present a poster, please note the details below and send your abstract electronically to arrive no later than 30 January 1998.

If you have indicated on your form that you are a student society member, you will automatically be considered for a poster award if you submit an abstract and present a poster. If you do not submit an abstract by the deadline, we cannot guarantee that there will be poster space.

How to submit an abstract

Abstracts should be sent ELECTRONICALLY, preferably by e-mail (as attachments or else in a text-only message) to (a.shirras@lancaster.ac.uk) or on diskette to:

Alan Shirras, Division of Biological Sciences
Lancaster University, Lancaster, LA1 4YQ, UK

Please identify your abstract in the following way: if sent as an e-mail message, please write Lancaster followed by your surname (add initials if it is a common name) as the subject field of the message. If your poster is intended for the BSCB session, please also add "BSCB" to the subject line. If sent on diskette or as an attached file, please name the file as Lancaster - (your surname), or a suitable abbreviation thereof if required by your word processor. If intended for the BSCB session, please write "BSCB" on the diskette.

Deadline for receipt of abstracts is 30 January 1998. Please do not enclose your diskette or a hard copy of the abstract with your registration form, which must be sent to a separate address.

Abstracts should be not more than 300 words, to fit inside a rectangle (16 cm across by 8 cm deep). Figures and diagrams must be capable of being printed on a black and white laser printer, and must fit within the allowed space. The abstracts will be made available to all participants in booklet form at the meeting. The text will not be retyped, so authors are responsible for the quality of presentation of the abstract. Any errors will appear in the reproduced text. Please draw our attention to any special characters or symbols, as these sometimes differ when transmitted or converted electronically.

Indicate, in the first line, the title and authors in capital letters. The name of the author who is responsible for the poster should appear first. Then indicate the laboratory where the research was done, the city, postcode and country.

BSCB Symposium

Cellular localisation – Functional microdomains within the cell

Organizers: Michael Whitaker and Peter Shaw

The symposium will ask the question: "What sorts of mechanisms set up regional differences inside plant and animal cells?" Although membrane traffic certainly play a part, this meeting will take a broader view of the mechanisms of cellular localization.

The BSCB meeting comprises five sessions, including a workshop. There will be a separate afternoon poster session. Additional speakers will be added to the main sessions from those submitting posters.

The workshop, 'Optical tools in living cells', will range in its topics from two photon confocal microscopy to using optical tweezers to microdissect cell components.

Wed 1st April, session I
Morning: Nucleus
Afternoon: Posters
Evening: Workshop I

Thurs 2nd April, session II
Morning: 'Functional colocalization'
Afternoon: Workshop II

Fri 3rd April, session III
Morning: Polarity

Speakers

I. Nucleus
Laskey (Cambridge) *Chromatin structure*
Lamond (Dundee) *Nuclear microstructure*
Greber (Zurich) *Nuclear pore regulation*
Misteli (Cold Spring Harbour) *Fluorescence visualization of RNA splicing*
Deng *Light-induced nuclear localization of transcription factors*

II. Functional colocalisation of molecular complexes
Bray (Cambridge) BORDEN LECTURER *Signaling complexes*
Meyer (Durham, NC) *Microdomain localization using GFP constructs*
Torok (London) *Calmodulin activation probes*
Highett (Boston) *Association of mRNA with the endoplasmic reticulum*
Jackson (Cold Spring Harbor) HAKE *Transport through plasmodesmata*

III. Polarity
Nurse (London) YAMANOUCHI LECTURER *Polarity mutants in S. pombe*
Petersen (Liverpool) *Polarity in calcium signalling*
Hepler (Amherst) *Pollen tube growth*
Drubin (Berkeley) *Profilin in yeast*

Workshop – 'Optical tools in living cells'

I. Imaging approaches
Steltzer (Heidelberg) / Bolsover (London) *Fundamentals of imaging*
Bastiaens (London) *Fluorescence resonance energy transfer*
Haseloff (Cambridge) *Green fluorescent protein*
Almers (Heidelberg) *Total internal fluorescence reflection microscopy*
Cannell (Auckland) *Two photon confocal microscopy*
Tumbar (Urbana) *GFP on chromosomes*
Firtel (La Jolla) *Transgenic aequorin*
Hanson (Ithaca) *GFP targetted to chloroplasts*
White (York) *Optical tweezers*
Graham Ellis-Davies (Philadelphia) *Flash photolysis (caged compounds)*
Jovin (Gottingen) *Time-resolved confocal microscopy*

BSDB symposium

Developmental Pathways

Organizer: Alan Shirras

Tuesday 31 March

Arrival and registration

Wednesday 1 April

9.00 *Plenary Lecture*: Richard Axel (New York)

10.00 Mathew Scott (Stanford) *Hedgehog/Patched signalling in development and cancer*

10.30 Tea/coffee

11.00 Henry Kronenberg (Boston) *Parathyroid hormone related protein and bone development*

11.30 Hans Clevers (Amsterdam) *β-catenin/TCF signalling in development and cancer*

12.00 Bruce Bowerman (Oregon) *Wnt signalling in C. elegans*

12.30 Lunch

14.00 Patrick Lemaire (Marseille) *Regionalisation of the amphibian organiser*

14.30 Andy McMahon (Cambridge, Mass.) *Signalling pathways in vertebrate limb morphogenesis*

15.00 Clive Dickson (London) *A role for fibroblast growth factor signalling in pregnancy dependent mammary gland development*

15.30 Tea/coffee

16.00 Pat Doherty (London) *Collaboration between cell adhesion molecules and growth factor receptors in neuronal plasticity*

16.30 Masatoshi Takeichi (Kyoto) *The role of cadherins in CNS wiring*

17.00 Andrew Tomlinson (New York)

18.00-19.30 Poster session

Thursday 2 April

9.00 *Yamanouchi Lecture*: Paul Nurse (London) *Polarity mutants in S. pombe*

10.00 Cathie Martin (Norwich) *The control of epidermal cell shape during petal development in flowers and the relationship to other types of epidermal specialisation in plants*

10.30 George Coupland (Norwich) *The transition from vegetative growth to flowering in Arabidopsis*

11.00 Tea/coffee

11.30 Caren Chang (Maryland) *The ethylene hormone-response pathway in Arabidopsis*

12.00 Jeff Wrana (Toronto) *TGFβ signalling and MAD-related proteins*

12.30 Irma Thesleff (Helsinki) *Signalling pathways in the regulation of tooth morphogenesis*

13.00 **AGM** and lunch

14.00 Vicky Rosen (Cambridge, Mass.) *Functional analysis of BMP receptors*

14.30 Ali Hemati Brinvalou (New York) *The molecular basis of vertebrate neural induction*

15.00 Norbert Perrimon (Boston) *Signalling pathways that regulate the cytoskeleton in Drosophila*

15.30 David Ish Horowitz (London) *Regulation of segmentation in flies and vertebrates*

16.00 Tea/coffee

16.30-17.30 Young Scientist Research Talks – six to be selected from abstracts

19.00 Conference Dinner, Jazz and Disco

Friday 3 April

9.30 Tony Hunter (La Jolla) *Signalling by receptor protein-tyrosine kinases and phosphatases*

10.00 Vasillis Pachnis (London)

10.30 David Wilkinson (London) *Role and regulation of Eph receptors and ephrins*

11.00 Tea/coffee

11.30 Tony Pawson (Toronto) *Modular protein interactions in tyrosine kinase signalling*

12.00 Jeff Williams (London) *The regulation of cellular differentiation in Dictyostelium by a STAT protein*

12.30 Lunch and end of meeting

BSCB/BSDB Spring Meeting

Lancaster University, 31 March – 3 April 1998

Name .....Prof / Dr / Mr / Ms

Address .....

.....

.....

Telephone ..... Fax ..... E-mail .....

Please circle details

Membership Status	Registration fee	Registration fee if poster presented (BSCB members only)
Society member	£50	£25
Student member	£15	Free
Non-member	£75	
Student non-member	£30	

Accommodation will be in Lancaster University residences with a choice of standard or en-suite room. The conference dinner is limited to the first 350. The registration fee includes the programme/abstracts booklet, tea/coffee, attendance at the scientific sessions and the social programme. Students have a reduced registration, **provided evidence of status is supplied with this form. There is a £25 reduction in registration fee for BSCB members who present a poster. Student members who present a poster are exempt from the registration fee. To receive this discount a COPY of the poster abstract must accompany this form (the original abstract must be submitted electronically). Only one reduced registration per poster.**

	Tue 31	Wed 1	Thurs 2	Fri 3	Totals
Lunch (£7.25/day)					£
Dinner, B&B, Standard (£29.35)					£
Dinner, B&B, En-suite (£37.85)					£
Conference Dinner supplement* (£20)			*		£
Registration					£
Late Booking Fee† (£20)					£
Member Package Standard (£160)					£
Member Package En suite (£185)					£
				Total	£

***Note:** Those not choosing a member package must pay a £20 supplement if they wish to attend the conference dinner. BSCB members presenting a poster may reduce the members package cost by £25. † The late booking fee will apply to forms received after **30 January 1998**.

Cheques should be made payable to "Lancaster University". Bank drafts must be IN STERLING, drawn on a UK bank and made payable to "Lancaster University". Credit cards are not accepted. No refunds will be given for cancellations made after 10th March.

Special dietary requirements ..... Car parking permit required

Return this form to **The Conference Centre, Lancaster University, Lancaster, LA1 4YT, UK.**
Queries Tel: 01524 592444

Forthcoming meetings

31 March 1998
RNA Extraction and Analysis
University of Hertfordshire

A one-day laboratory/lecture course

Details from:
Dr Ralph Rapley,
Department of Biosciences,
University of Hertfordshire,
College Lane, Hatfield,
Herts AL10 9AB
UK.

Tel: (01707) 284513
Fax: (01707) 284510
E-mail: r.rapley@herts.ac.uk

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1 April 1998
PCR Methods and Applications – A one-day laboratory/lecture course
University of Hertfordshire

Details from:
Dr Ralph Rapley
Department of Biosciences
University of Hertfordshire
College Lane, Hatfield
Herts AL10 9AB
UK.

Tel: (01707) 284513
Fax: (01707) 284510
E-mail: r.rapley@herts.ac.uk

6–9 April 1998
Molecular Biology Update
University of Hertfordshire

A laboratory-based course

Details from:
Professor John Walker,
Department of Biosciences,
University of Hertfordshire,
College Lane, Hatfield,
Herts AL10 9AB
UK.

Tel: (01707) 284546
Fax: (01707) 284510
E-mail: J.M.Walker@herts.ac.uk

15–16 July 1998
Antimicrobial Agents
University of Hertfordshire

A two-day introductory laboratory course

Details from:
Dr Ian Morrissey,
Department of Biosciences,
University of Hertfordshire,
College Lane, Hatfield,
Herts AL10 9AB
UK.

Tel: (01707) 285163
Fax: (01707) 285046
E-mail: i.morrissey@herts.ac.uk

20–24 July 1998
Epitope Mapping
University of Hertfordshire

A laboratory course

Details from:
Professor John M Walker,
Department of Biosciences,
University of Hertfordshire,
College Lane, Hatfield
Herts AL10 9AB
UK.

Tel: (01707) 284546
Fax: (01707) 284510
E-mail: j.m.walker@herts.ac.uk

July 1998
Cellular Senescence: the future of ageing
Oriel College, Oxford University

BSCB workshop. Dates to be confirmed.

Local organiser: Lynne Cox (Oxford).
Other organisers: David Kipling (Cardiff), Richard Faragher (Brighton), Ian Kill (Brunel).

Limited to 50 places; early applications welcomed. Please mail enquiries to Lynne Cox on lscox@bioch.ox.ac.uk

13–16 September 1998
Epithelial Cell Biology '98
St Catherine's College, Oxford University

Epithelial Cell Biology '98, a 2-day meeting organised by Paul Edwards (Cambridge) and Charles Streuli (Manchester), will bring together some of the world's most distinguished biologists to discuss such topics as:

- epithelial cell fate and morphogenesis
- cell-matrix and cell-cell signalling
- oncogenes and tumour suppressors in epithelial carcinogenesis

For further information see the meeting Web page
http://www.path.cam.ac.uk/~pawe1/BSCB98.html
where the programme and registration details will be posted later this year.

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15 September 1998
Molecular Probes in Diagnostics
University of Hertfordshire

Nucleic acid and protein techniques

Details from:
Dr Ralph Rapley,
Department of Biosciences, University of Hertfordshire,
College Lane, Hatfield,
Herts AL10 9AB
UK.

Tel: (01707) 284513
Fax: (01707) 284514
E-mail: r.rapley@herts.ac.uk

Young Cell Biologist of the Year Poster Prize 1998

WIN A TRIP TO SAN FRANCISCO

Win a trip to the American Society for Cell Biology 38th Annual Meeting and show your work.

All research students are invited to enter the next poster competition at our Spring 1998 meeting at the University of Lancaster, 31 March to 3 April 1998 (main symposia: Cellular localisation – Functional microdomains within the cell). The prize is a trip to the USA to attend the 1998 ASCB meeting, to be held in San Francisco, December 12–16 1998, as their guest, with an opportunity to present the winning poster. Please enter!

The poster will be judged on scientific merit and presentation by a panel of British and American cell biologists.

You are eligible to enter of you are a full-time PhD student registered at a British Institution and a member of the BSCB.

Complete the form below and return it to the Secretary, Birgit Lane, CRC Laboratories, Department of Anatomy and Cell Biology, Medical Sciences Institute, University of Dundee, Dundee, DD1 4HN

Name:

.....

University and Department

.....

.....

Year studies commenced

.....

Address of planned postdoctoral position,

if known:

.....

.....

.....

Date of commencement of BSCB membership:

.....

Present academic address for correspondence

.....

.....

.....

.....

E-mail address:

.....

Honor Fell Travel Awards

Honor Fell Travel Awards are made, up to a limit of £250, to provide financial support for young BSCB members to attend meetings. Applications are considered for any meetings relevant to cell biology.

Applications (including a copy of the meeting registration form) should be sent to David Edgar (address on page 32) using a copy of the form below.

The following rules usually apply (at the discretion of the Committee):

- Awards are not normally made to applicants aged over 35
- Applicants must have been BSCB members for at least a year.
- No applicant will receive more than one award per year or three *in toto*.
- The applicant must be contributing a poster or talk

Application for an Honor Fell travel award

Name: .....

Age: .....

Work address: .....

.....

.....

..... Postcode: .....

E-mail address: .....

Degrees (with dates):

.....

.....

Present position (graduate students give start year of PhD): .....

.....

.....

Date of joining BSCB: .....

Record the years of previous Honor Fell awards (if any): .....

Key publications (2) or research interests:

.....

.....

.....

.....

Meeting for which application is made (Title, place, date): .....

.....

.....

Estimated expenses: Travel: .....

Subsistence: .....

Registration: .....

Other: .....

Have you submitted any other applications for financial support?: YES NO

If yes, please give details: .....

.....

Number of meetings attended last year: .....

Supporting statement by Head of Department:

The applicant requires these funds and is worthy of support

Name: .....

Signature: .....

Applicant's signature: .....

Date: .....

ADVERTISING WITH THE BSCB

(Membership approx. 2000)

Newsletters – Summer and Winter

Current Charges

Single advertisement:

Back cover Black and White £275; Colour £425
Inside front cover Black and White: £275
Full inside page, black and white only £220
1/2 Inside page, black and white only £110
1/4 Inside page, black and white only £55

For four advertisements, which would cover two years, the costs would be reduced by 30%.

We are also happy to enclose flyers with the Newsletter. For a single page, the cost is £165; additional pages are £50.00. For booklets, we negotiate on weight.

Mailing List (Peel-off Labels) – £225.00 + p&p

Advert copy is required in October for Winter Publication, April for Summer Publication

Please supply either:
electronic file of your advert together with hard copy artwork
or: film – single/four-colour positive, right reading, emulsion down, screen 133/150

Contact: Margaret Clements
Tel: (44) (0)1223 336655;
Fax: (44) (0)1223 353980
Department of Zoology,
Downing Street,
Cambridge CB2 3EJ

Trade Exhibitor space at Symposia available on request (contact Meetings Secretary)

Application to join the BSCB

Please complete and return this form and the one on the following page to:
Birgit Lane, BSCB Secretary CRC Laboratories, Department of Anatomy and Physiology, University of Dundee, Dundee DH1 4HN.

Name: ..... Sex: .....

Position: .....

Academic qualifications: .....

Tel: ..... Fax:..... E-mail: .....

Work address: .....

.....

..... Postcode: .....

Research interests (5 keywords): .....

.....

Membership of other scientific societies: .....

.....

BSCB member proposers (names and signatures):

1) .....

2) .....

Applicants without proposers should enclose a brief curriculum vitae.

Applicant's signature: ..... Date: .....

The Society does not employ professional administrators, so payment by **DIRECT DEBIT** would be appreciated (**please photocopy and fill in the form on page 29**). For overseas members, or those for whom this is not possible, a cheque in pounds sterling should be sent to the Secretary. Members will be responsible for renewals without reminders.

Instructions to your bank/building society to pay direct debits

Please complete parts 1 to 6 to instruct your branch to make payments directly from your account. Then return the form to:

BRITISH SOCIETY FOR CELL BIOLOGY, C/O DR BIRGIT LANE, CRC LABORATORIES, DEPARTMENT OF ANATOMY AND PHYSIOLOGY, UNIVERSITY OF DUNDEE, DH1 4HN.

To The Manager,

Originator's identification number

9	4	1	4	5	1

1. Please write the full postal address of your branch in the box above.

2. Name of account holder

.....

3. Account number

4. Sort code — —

Banks/Building Societies may refuse to accept instructions to pay direct debits from some types of account.

5. Originator's reference number (for office use only)

BRITSO

6. Instructions to the Bank or Building Society

Please pay the British Society for Cell Biology Direct Debits from the account detailed on this Instruction subject to the safeguards assured by the Direct Debit Guarantee.

Signature .....

Date .....

Standing order cancellation

Please cancel any standing order payable to the British Society for Celi Biology WITH IMMEDIATE EFFECT.

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Account Number

Customer's Account Name

Branch Sort Code — —

Signature .....

Date .....

The Direct Debit guarantee

- This guarantee is offered by all Banks and Building Societies that take part in the Direct Debit scheme. The efficiency and security of the scheme is monitored and protected by your own Bank or Building Society.
- If the amounts to be paid or the payment dates change you will be told of this in advance by at least 14 days.
- If an error is made by the BSCB or by your Bank/Building Society, you are guaranteed a full and immediate refund from your branch of the amount paid.
- You can cancel a Direct Debit at any time, by writing to your Bank or Building Society. Please also send a copy of the letter to the BSCB.

Membership fees for 1997

£20.00	**for regular membership paid by DIRECT DEBIT**
£25.00	**for membership paid by cheque**
£8.00	**for student membership paid by DIRECT DEBIT** **for those paid the equivalent of a postgraduate student grant**
£12.00	**for student membership paid by cheque**

Discount on journal subscriptions

BSCB members can receive the following journals at discounted subscription rates:

	Full rate	**Members rate**
Journal of Cell Biology	US$165.00	US$125.00
Bioessays	£73.00	£63.00
Journal of Experimental Biology	£122.00	£112.00
Journal of Cell Science	£118.00	£110.00
Development	£169.00	£151.00

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Fax: 01533 523369
e-mail: drc@leicester.ac.uk

Margaret Clements

For mailing address changes, to place an advertisement or for any general enquiries, please contatct the BSCB assistant:

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Downing Street
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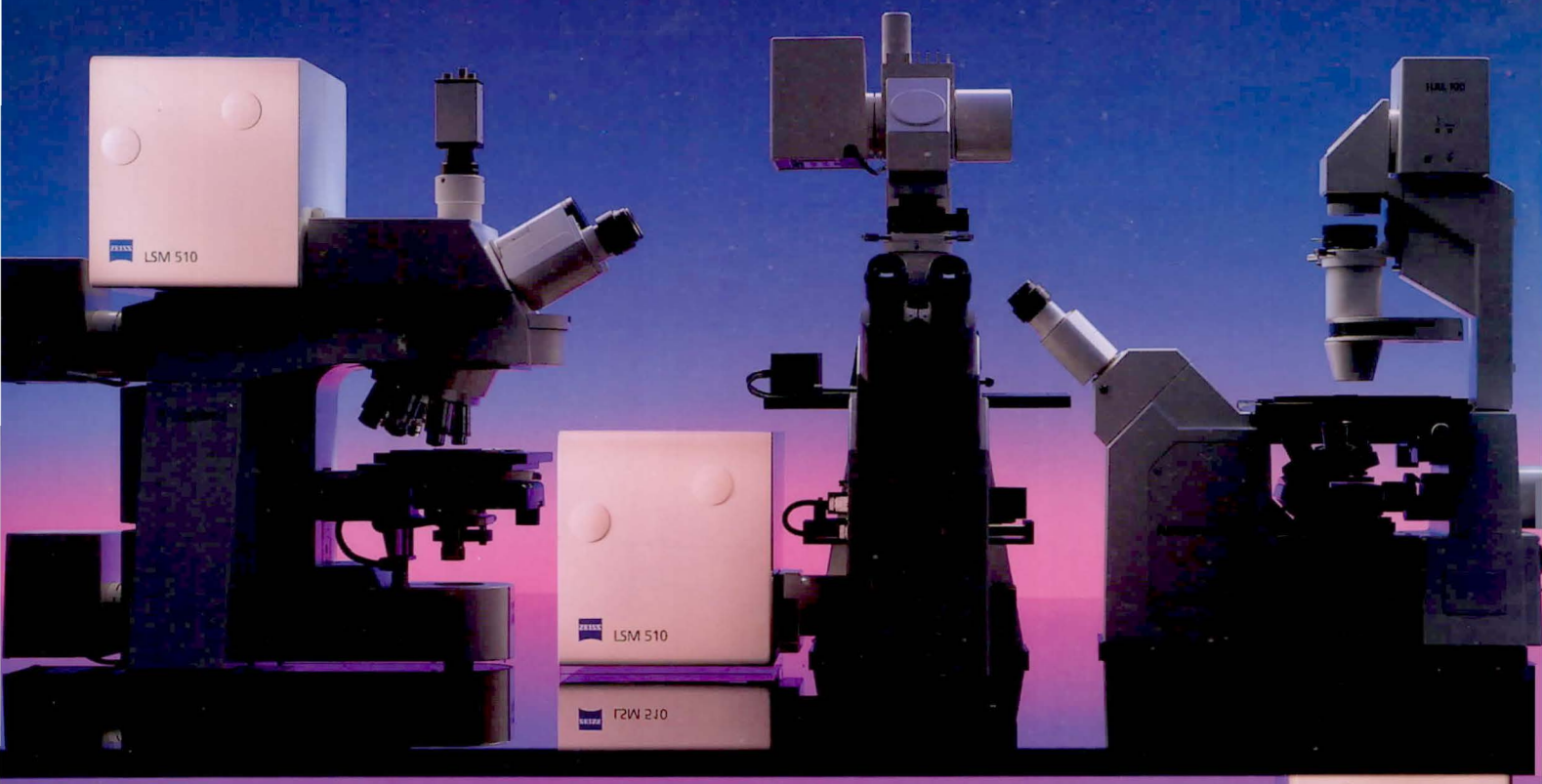
Tel: 01223 336655.
Fax: 01223 353980.
E-mail: zoo-jeb01@lists.cam.ac.uk

down. . .side . . .up



up. . .side . . .down

It's flexible, I'll say that. Look how it interchanges between both upright and inverted microscopes - always using the shortest possible light path.
Compact too. They tell me there are six detectors inside, but it looks far too small.
With four simultaneous confocal channels, each with its own computer controlled pinhole, it's ideal for my multi-parameter fluorescence work.
Let's have a look at the operating system. Windows NT, the latest, with multi-user software. 'Open' software too, for me to build my own application programmes. It seems perfect for everybody.
What about the image? They say 2048 x 2048 pixels and 12 bit dynamic range - the ultimate resolution with highest possible sensitivity.
Let's take a look. Wow! That's sharp, what depth and range: just what I need for my experiments!
Integration, oversampling, quasi-photon counting - the people at Carl Zeiss have thought of everything.
Now, which way round shall I use my new LSM 510. . .
. . .Down?. . Side?. . Up?

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