

Swiss Light Microscopy Facilities: A Success Story for the last Fifteen Years

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Abstract: Core light microscopy facilities have been established at most major Swiss universities and research institutes. Their modern and technically diverse equipment is primarily dedicated to in-house users, but opens increasingly to externals from other academic institutions as well as from the private sector. A recent survey of Swiss light microscopy facility managers enabled an analysis of the challenges involved in the running of such facilities and highlighted their scientific and economic impact within their home institutions and beyond.

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Introduction

Over the last one to two decades, Swiss research institutes and universities have been establishing an increasing number of core facilities bundling infrastructure, to enable the efficient use of increasingly complex and costly equipment for fundamental research.

From the very beginning light microscopy facilities were at the very center of this effort and are now well-established players at their host institutions giving access to an ever-increasing range of cutting edge imaging technologies.

In the first part of this review I will concentrate on describing the landscape of Swiss light microscopy facilities and will detail the motivations that led to their establishment, their mode of functioning and list their resources (Fig. 1).

In the second part of this review I will present the results of a recent survey that was sent to all Swiss light microscopy facility managers asking them to answer questions concerning usage of their facili-

ties by discerning in-house versus external users and define the format of this usage. Questions were targeted to get feedback on past experience as well as for the openness of facilities to future collaborations. Importantly questions distinguished between academic and non-academic access.

I did not include the field of electron microscopy facilities in the current review although it would be equally interesting to describe and evaluate their functioning.

The Beginnings: Establishing Swiss Light Microscopy Facilities

In biology, visualizing cells and tissues by light and equally electron microscopy has led to a multifold of important discoveries and use of microscopes and other imaging technology became increasingly important.

Until the end of the nineties it was mostly individual laboratories and re-

search groups that ‘owned’ one or several microscopes and individual researchers of the respective groups were ‘the experts’ who knew how to use these instruments. In some instances, instruments were already shared but if so then at most at the department level.

As seen in the chart (see Fig 2), the number of publications with microscopy in its title or abstract was relatively stable from the mid-eighties until about 1998 with about 10000 publications per year. From then the number increased steadily hitting the 30000-mark in 2013. Concomitant with the beginning of this increase, the first light microscopy core facilities were starting to be created at the beginning of the century. In our case for example at the University of Geneva the microscopy facility was created in 2002 within the newly established NCCR (National Center of Competence in Research) ‘Frontiers in Genetics’. This was done as part of its mission to create new research infrastructure.

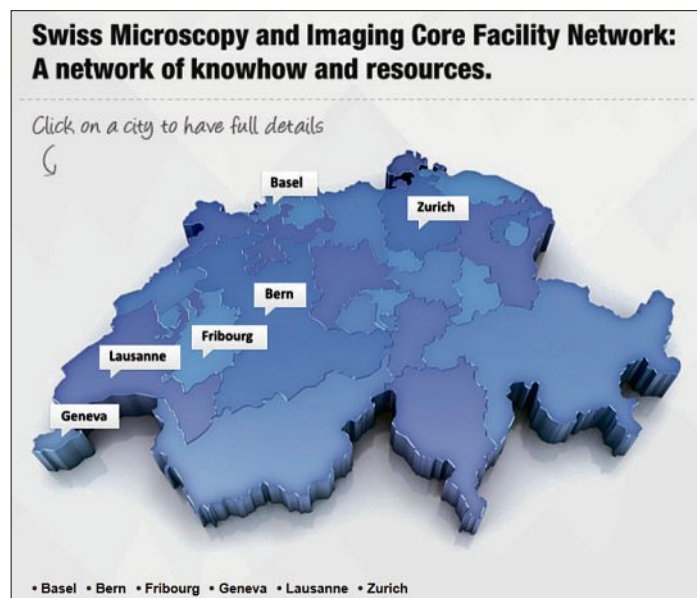


Fig. 1. Map showing Swiss cities with major light microscopy facilities. For details see website: www.swissbioimaging.org

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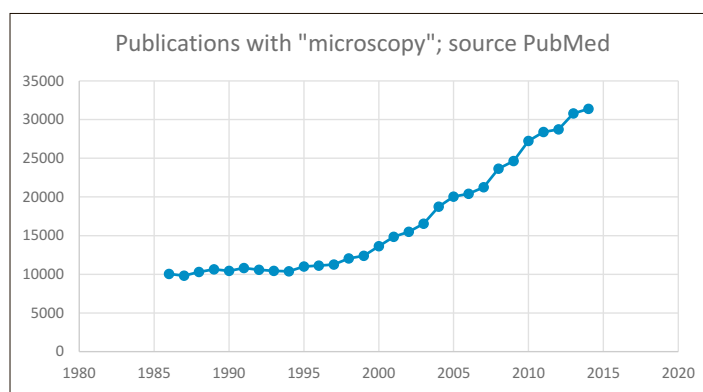


Fig. 2. Graph showing the annual number of publications containing the keyword 'microscopy' in title or abstract. Source PubMed.

In other instances, new facilities were created by regrouping already existing instruments.

Beside bringing new or existing instruments together it was important that these newly-established facilities were concomitantly staffed with qualified personnel. This was at the beginning often only one person taking care of instruments and teaching users how to use them. As the definition of a 'light microscopy facility manager' was just started to be defined, it was often talented post-docs with knowledge and dedication to microscopy who became the first of their kind.

In the meantime, many Swiss light microscopy facilities have increased their staff and have often even specialized personnel dedicated to a certain subject like image analysis or specimen preparation. In the same time, ours and other Swiss light microscopy facilities who have started fifteen years ago with only one or two microscopes have now reached numbers of 15 to over 25 instruments.

The motivation to build and finance light microscopy facilities was multifold:

1. Costs of instruments: As instruments were becoming more sophisticated raising purchasing and maintenance costs, there was an increasing interest to maximize their usage by making them available to a larger group of users.
2. Establishing new technology: A larger user group with the consequence of a heavier instrument usage made it easier to justify a regular turnover and replacement of outdated instruments. Turnover of instruments became of key importance as microscopy technology advanced very rapidly and a microscope could become outdated within only a few years. As an indication for the rapid innovation in this field is the fact that the number of patents containing the keyword 'microscopy' has more than doubled between 2007 and 2014 and has reached over 700 such patents per year in 2014 (Fig. 3). Another indication for this can be taken from the fact that four out of the last

eight 'methods of the year' as defined by the journal *Nature Methods* were microscopy-related.

3. Complexity of instruments: As a consequence of these rapid and continuous innovations, microscopy instrumentation became more and more complex. This resulted in the wish for having dedicated imaging and microscopy specialists to maintain instruments and train users on how to efficiently use them.

Taken together the above-mentioned reasons were the driving force for the creation of new light microscopy facilities which are now found in practically all Swiss universities and research institutes. The location of Swiss light microscopy facilities is by nature correlated with larger Swiss cities and their respective universities and institutes (Fig. 1). One exception is the Paul Scherrer Institute (PSI) which is located in Villigen in a more rural area of the canton of Aargau (not indicated in the map of Fig. 1).

What are Swiss Light Microscopy Facilities Offering: Instrumentation and Scope of their Service

The primary goal of technological facilities is to serve their host institution and local community by offering technological infrastructure.

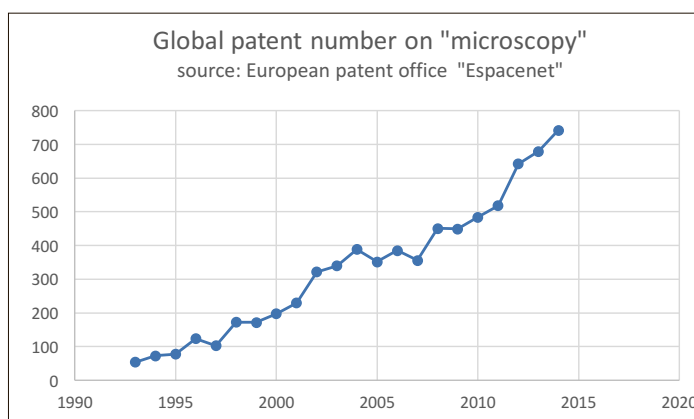


Fig. 3. Graph showing annual number of worldwide patents containing the keyword 'microscopy'. Source: European Patent office.

In a recent survey that was sent to Swiss light microscopy facilities and which was answered by twelve facility heads, a total number of over 3000 accounted and active users was indicated. This represents an average number of about 250 users per facility.

Concerning instruments located in Swiss light microscopy facilities, the total number of instruments was 203 or an average of 17 instruments per facility. The last time the overall number had been accounted for was in 2012 where it was 149. This means that the number of instruments increased by about 26% in only four years. This shows that instruments are continually added.

Another important indication is the turnover of instruments. Currently about 40% of the instruments located in Swiss light microscopy facilities are 5 years-old or younger. This indicates that in addition to adding new instruments, old equipment is regularly updated and replaced.

The financial investment that these instruments represent can only be roughly approximated. Starting from a very conservative estimate of 300'000 Swiss francs per instrument we arrive at a total investment volume of about 60 Million Swiss francs or an average of 5 Million Swiss francs per facility for instruments only.

Instruments listed and offered at Swiss light microscopy facilities are in general complex instruments such as workstations for multidimensional imaging, confocal microscopes, light sheet fluorescence microscopes or super-resolution instruments. Standard transmission and fluorescence microscopes are also present at facilities but more to complete their instrumentation as these instruments are often already found at the department level or in individual research groups. Additionally, facilities often offer some key technologies exclusive to them or rare to find elsewhere. For these techniques users cross over and go and use other facilities than the ones at their home institutions. This cross-usage is very easy to organize and all Swiss light microscopy facilities are either already do-

ing it or are open to do it in the future (see more details below in the last section under 'External Usage').

At our facility at the University of Geneva for example we specialize in bioluminescence microscopy. For this technique firefly and other luciferases with their respective substrates are used as gene expression vectors and bioluminescence signals are detected at single cell resolution in a dedicated bioluminescence microscope (Fig 4).

One important mission of light microscopy facilities is education and training of users. All Swiss light microscopy facilities do one-to-one sessions to train users in the use of a specific instrument or technology. In addition, most facilities offer additional microscopy courses to their internal users or as part of the teaching program of their institutions with some of these courses being accessible for external users. A few of the websites listing courses offered by Swiss light microscopy facilities are listed at the end of the article.

How are Swiss Light Microscopy Facilities Managed: Investments, Running Costs, Human Resources and Income Schemes

As seen in the previous chapter, significant investments for equipment and instrumentation have been undertaken at Swiss light microscopy facilities. These investments are a continuing effort as a) instruments are being replaced and b) new techniques are integrated and increase the technical portfolio offered to the users. If we take the above numbers of an average of

5 million Swiss francs worth of instrumentation per facility and a turnover of 40% within 5 years a sum of 400'000 Swiss francs of investment into instruments is needed annually to maintain a facility at its status quo.

This sum might often be insufficient when it comes to instruments offering newly-developed technologies such as superresolution imaging, fluorescence lifetime analysis or the latest light sheet illumination techniques. Such instruments are often priced at up to one million Swiss francs or more. To integrate and offer new and/or more complex technologies at a facility thus demands financial efforts well above the aforementioned 400'000 Swiss francs.

Maintenance costs represent another important part of the facilities budget. If we use 4% of instrument purchasing costs as the annual costs for their maintenance, we arrive at an additional sum of at least 200'000 Swiss francs needed annually at each facility. Not reflected in this calculation are costs for software and IT infrastructure. These costs are significant and can reach from 100'000 to several 100'000 Swiss francs annually.

At the 12 light microscopy facilities that have responded to our survey the average number of staff per facility was 3.5 full time positions. For this I did not take into account staff working for electron microscopy in mixed facilities but only those working for light microscopy and/or image analysis. With an average salary of 85'000 Swiss francs per person (plus 20% social benefits of 17'000 Swiss francs) the costs for 3.5 staff positions are at 357'000 Swiss francs per year. In total, each Swiss light

microscopy facility thus has average running costs of about 550'000 Swiss francs (maintenance plus salaries) not including software, IT- and other infrastructure (buildings, electricity, *etc.*).

Concerning financial funding and income, the individual Swiss light microscopy facilities have very different schemes. Normally funding comes from three different sources namely: a) the home institutions, b) funding agencies and c) usage related payments (user fees). User fees are often not static but depend if users come from in-house, from other academic institutions or from the private sector (companies). Several facilities are, for example, totally free for in-house users. In other facilities user fees are asked and used to partially cover the aforementioned running costs of the facilities. Currently none of the Swiss light microscopy facilities is totally auto-financed, *i.e.* investments, maintenance and salaries are covered by user fees only. Usage fees currently range from 10 Swiss francs per hour for a basic microscope for in-house users to up to several hundred francs being asked from companies, for example, for the use of a complex superresolution instrument.

As mentioned all Swiss light microscopy facilities depend currently on funding to cover running costs (salaries, *etc.*) and normally equally for the investment costs for equipment (instruments). Especially the latter often require support from funding agencies. One possibility for funding are so-called R'Equip grants from the Swiss National Science Foundation (SNF). These grants are dedicated to the acquisition of large-scale instruments, where the SNF covers 50% of the purchasing costs and the other half rests with the home institution plus eventually other local funding agencies (public or private). At our facility at the University of Geneva for example a R'Equip grant obtained by the academic director of the facility Marcos Gonzalez-Gaitan enabled the purchase of a super-resolution STED confocal microscope: an investment worth about 1 million Swiss francs.

Reaching Beyond: Past and Future External Usage of Swiss Light Microscopy Facilities

A part of our survey asked questions related to the usage of Swiss microscopy facilities for external users. All facilities answering our survey had already given training and instrument access to users coming from other academic institutions. Surprisingly ten out of twelve facilities had also given these forms of access to the private sector (companies). Asked if they were open to repeat these forms of access

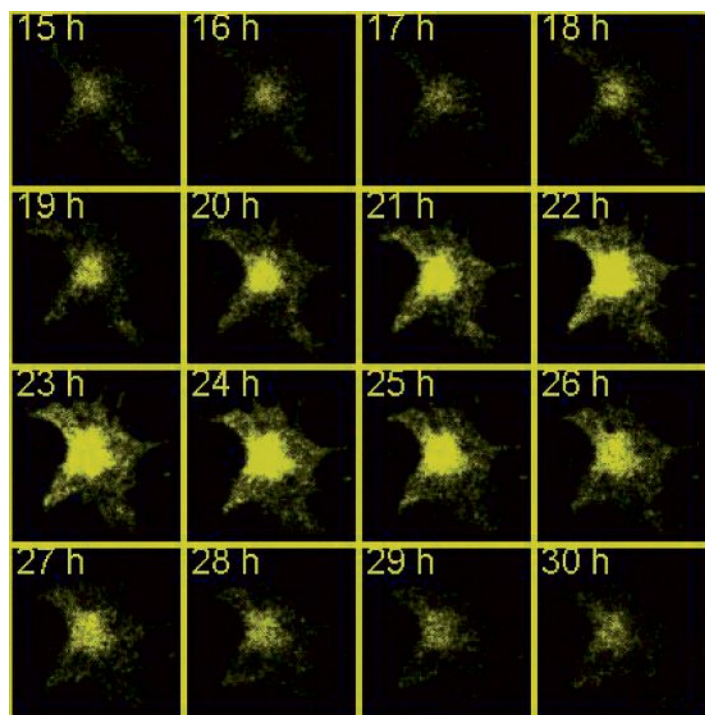


Fig. 4. Bioluminescence microscopy research from Ueli Schibler's lab at the University of Geneva showed that expression levels of circadian genes peak every 24 hours. Images presented above were taken from a time-lapse experiment and show circadian (Bmal1-) driven luciferase expression in NIH3T3 mouse fibroblasts.. Bmal1-luc was engineered originally by S. A. Brown, F. Fleury-Olela, E. Nagoshi, C. Hauser, C. Juge, C. A. Meier, R. Chichestortiche, J.-M. Dayer, U. Albrecht, U. Schibler, *PLoS Biology* 2005, 3, e338.

in the future all facilities were ready to do this including those that had not already done it in the past. This said it was also stated that facilities are obliged to prioritize their in-house users and that they can only receive external users within the limits of availability of instrument and personnel.

This was equally reflected when asked if facilities were open to offering a full service. Full service means that complete assays from specimen preparation, to imaging, to image analysis are performed by the staff of the respective facilities. Only five out of twelve facilities were considering this kind of service to users from other academic institutions and four were open to also offer this to the private sector.

At our facility at the University of Geneva we have had, over the years, several collaborations with companies from small startups to large multinationals. Most of these collaborations were actually either on the level of full-time (permanent) support of the users or as a full service where the entire experiment would be designed and conducted at the facility with the companies receiving a written report. This kind of collaboration clearly demands a relatively important amount of time and effort from the facility staff. On the other hand, it can serve as an additional source of facility-income as hours spent for these collaborations can be billed at industry rates.

It is very important for both partners of such collaborations that these are based upon well-defined contracts detailing the goal, scope and limits of the service. At the university of Geneva, a dedicated technology-transfer office helps to shape and define such contracts.

Challenges

Although light microscopy facilities are well established in Switzerland they are still facing two major challenges. The

first challenge is funding. In most facilities user fees cover not even the pure running costs (service maintenance and repair) of the equipment. To purchase new instruments and technology as well as to replace outdated equipment extra funds have to be found. For most Swiss light microscopy facilities these funds do not come automatically but they need to be claimed to their home institutions and/or through grant applications (for example R'Equip as mentioned above). The difficulties involved for installing new technology is often the very high price tag. Still, funding agencies seem to be from our experience more open to financing new and fancy technology than to just replacing existing equipment that is only outdated. So updating of instruments is for many facilities a continuous battle.

The second challenge is personnel. When light microscopy facilities were newly established, contracts for facility managers and staff people were mostly temporary and their status ill-defined. This situation has somewhat improved. Nonetheless it is still difficult to convince local administrators of the need to increase personnel, for example, and hire a dedicated imaging analysis specialist. As a consequence, the number of staff working in a given facility is often at the extreme limit. Out of twelve Swiss light microscopy facilities, five are staffed by only one or two people (including the facility manager).

Summary

Light microscopy facilities have been established at essentially all major Swiss universities and research institutes. Overall the equipment at Swiss light microscopy facilities is modern and of vast technical diversity demonstrating a rapid assimilation of new technology. Challenges are funding of new and replacement of existing (outdated) instruments as well as finding and financing of qualified staff.

Swiss light microscopy facilities are open to external users and are happy to give access to their instrumentation and teach their usage not only to users from other academic institutions but equally to those coming from the private sector (companies). Currently only a minority of facilities offer or consider to offer collaborations in form of a full service. One reason for this could come from the rather tight staffing situation that most facilities are facing. So companies interested in using the service of a Swiss light microscopy facility should currently consider sending personnel to the facility rather than counting on having a full service.

In summary we can state that Swiss light microscopy facilities as certainly many other facilities (such as electron microscopy, *etc.*) are being recognized as partners and indispensable elements at their home institutions and are valued as a central part of research infrastructure available to local users and beyond.

Websites Offering Courses at Swiss Light Microscopy Facilities

<https://microscopynetwork.unibas.ch/home/>

The Basel microscopy network list courses and workshops offered at seven light and electron microscopy facilities at Universities and research institutes in and around Basel. Access from outside users to these courses needs to be negotiated.

www.ls2.ch

The Union of Swiss Societies for Experimental Biology (USGEB) known today as Life Sciences Switzerland (LS2) lists and supports financially a number of workshops and seminars related to Life Sciences in Switzerland. The list includes several microscopy-related courses and events and can be downloaded from the site.

<http://www.swissbioimaging.org/>

Site listing Swiss microscopy facilities (light microscopy and others) with links to their equipment and to their individual websites.

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