



PALM[®] MicroBeam HT

A Promising Perspective for the Pharmaceutical Industry

A report by Hermine Hitzler PhD • P.A.L.M. Microlaser Technologies



The pharmaceutical industry is, at the moment, in a phase of change. Health care costs are exploding, the validity of many lucrative patents is about to expire, and competition becomes stronger forcing the industry to bring out new products and ideas. Due to what seems the end of the Golden Age of biotechnology (which has been celebrated as the basic technology at the end of the 20th century), venture capitalists are skeptical and can only be convinced of innovative new ideas and designs by conclusive approaches.

It is clear that, in the present situation, cost saving aspects come to the fore. A great potential for this can be found in the field of development, especially when the development times – i.e. the processes of screening and evaluation in the preclinical phases – can be reduced. This becomes possible when a quicker implementation of new technologies in the standard processes for drug screening and testing can be realized. The plenty of newly available technologies in micro-handling of biological objects – with objects ranging from samples extracted from histological slides to even single living cells – combined with the automated dosage of components in the nano- and picoliter range allows a considerable increase of throughput in fully automated processes.

• **New Technologies Search for New Challenges**

The mapping of the human genome resulted in a lot of new possible therapeutic targets. Research in deep seas and in virgin forests permanently yields new possible drug components. Thus, an abundance of possibilities for testing are available and the main question is about efficiency and reliability of screening.

Individual medicine, better described as patient specific drug design, is no longer a catch phrase with these new technologies but meanwhile a realistic alternative and somewhat of a lifesaver or last resort for people who do not respond to standard drug therapy or suffer from severe side effects. Especially for these patients, quick development procedures are vital and can be realized with the current available technologies.

Challenges to be met are: a highly pure sample preparation and a reliable tracking during the high throughput handling. P.A.L.M. has accepted this challenge and supplemented the well tried and established PALM[®] MicroBeam with the PALM[®] RoboMover – a device for automated high throughput handling of standard microtiter plate formats. Thus P.A.L.M. can offer a platform for microdissection and contamination-free sample generation in screening and high throughput processes.

- **The LMPC Technology: Clear Cut Gap and Laser Pressure Catapulting**

Generation of highly pure samples is a prerequisite for modern drug evaluation and testing on molecular basis. Different methods of microdissection are the modern tools for sample generation from the pool of possible drug candidates and targets.

Among today's largely available devices, P.A.L.M. offers the most advanced technology in terms of high purity of the samples and versatility of the device. The powerful laser based technology enables the circumscision of the desired sample creating a clear cut gap between the sample and its surrounding tissue. Then the circumscised sample is lifted up into a collecting vessel only with the help of light: the complete process of sample generation, which is called Laser Microdissection and Pressure Catapulting (**LMPC**), is non-contact and thus contamination-free. The complete molecular information of the sample is preserved unchanged and can be decoded in subsequent analyses, e.g. in genomic and proteomic studies. As most biological objects are transparent for the applied laser wavelengths, it is possible to work even inside living cells without disturbing its viability.

The lasers used (a pulsed UV-A cutting laser and a continuously emitting infrared laser for optical trapping, both of high beam quality) are interfaced into high quality microscopes and focused through objectives with a high numerical aperture to a minimum possible spot size. LMPC can actually be applied to living organisms: it has been shown that even *C. elegans* could be transported by light into appropriate collecting vessels without losing its vitality.

- **The P.A.L.M. Product Family: PALM[®] MicroLaser Systems**

The PALM[®] MicroLaser family of products is a collection of up-to-date tools for precise, non-contact laser based micromanipulation as it is needed in all areas of medical and pharmaceutical research. The devices allow not only microdissection, i.e. cutting and ablating in microscopical samples, but also to catch and move objects in a liquid environment.

The range of products is starting with the PALM[®] MicroBeam as the center piece. The PALM[®] MicroBeam is the state-of-the-art device for modern Laser Microdissection and subsequent Pressure Catapulting (**LMPC**). It is intended for the collection of precisely defined cells (living or fixed) or subcellular particles from all kind of samples as they routinely are used in pathology, oncology, neurology or are needed for proteomics and cytogenetics as well as genetic engineering or other fields of biological, medical or pharmaceutical research.

The PALM[®] MicroBeam is available in several modifications. The image processing model MicroBeam IP has already been developed according to the needs in pharmaceutical research. This device combines the proven technology of non contact laser manipulation and pressure catapulting with the most advanced image scanning software features.

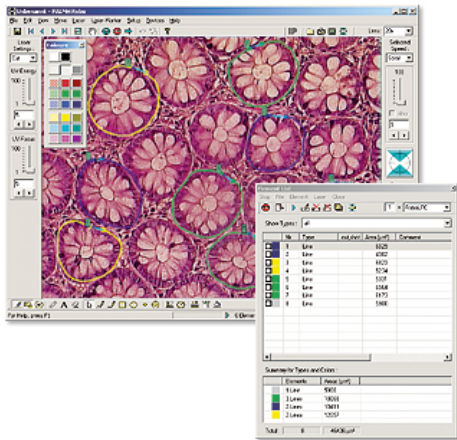
In the newest PALM[®] MicroBeam generation, the high throughput model PALM[®] MicroBeam HT, the experience of 10 years in microdissection is incorporated. The combination of non-contact microdissection with automated target identification of rare cells and specific tissue and target capture is especially conformed to the needs in high throughput applications as they are standard in drug research.

The PALM[®] MicroTweezers is the main product for catching and moving particles in liquids. As a combination of PALM[®] MicroBeam and PALM[®] MicroTweezers, the PALM[®] CombiSystem combines the cutting properties of the PALM[®] MicroBeam with the trapping and manipulation capabilities of the PALM[®] MicroTweezers and adds up to an all-purpose working station for the manipulating treatment of all kinds of microscopic particles. Only the forces of light are used to cut, catapult, trap, sort or position with extremely high precision.

To realize these ambitious intentions regarding the high precision, P.A.L.M. developed components like the PALM[®] RoboStage. This is a motorized, computer-controlled microscope stage, allowing object positioning with submicron precision and enables partly automated micromanipulation procedures. The new generation PALM[®] RoboStageII offers the possibility to use customized sample holders, e.g. for microtiter plates and multiwell plates or, in combination with special software functions, even serial sections from one sample by linking up to four slides.

The tailor-made collecting device to the PALM[®] RoboStage II is the PALM[®] RoboMover: the combination of both allow high speed microdissection of the samples combined with high speed collecting of the microdissected sample pieces and areas into a variety of customized collecting devices like microtiter plates, chips and wafers. This is a prerequisite for establishing microdissection as a standard procedure in high throughput processes.

- **Special Software Features for Special Applications**



The heart of the PALM[®] MicroLaser Systems is the very sophisticated PALM[®] RoboSoftware. From the first beginnings, it was conceived for the special needs in microdissection and within 10 years of experience in this field, it has matured to a multifunctional tool offering all possibilities in a user-friendly and self-explaining interface. Different cutting routines for glass- and membrane-mounted sections can be chosen to use optimized working conditions from the first laser shot. With a plenty of drawing tools, cells or sample areas can be preselected automatically and then be assigned to special collection vessels. With a mouse click, the system is able to perform the cutting and catapulting actions.

Even critical work under fluorescence observation is easily realized with the PALM[®] RoboSoftware due to a cleverly devised fluorescence shutter mode (*freeze mode*) allowing

sample preselection in the frozen image to avoid bleaching effects. **LMPC** is possible under direct fluorescence illumination (requiring special filter sets) or in the standard mode after sample preselection with the *freeze mode*. Thus, all available standard fluorescence filter sets can be used.

- **PALM[®] MicroLaser Systems: All Possibilities in One Device**

The PALM[®] MicroLaser Systems are built up in a modular concept. Only high quality research microscopes are used for the complex devices. P.A.L.M. developed special lens and mirror holders since common available products do not provide the required precision. This ensures that the laser beam path is in parallel to the optical axis of the light microscope and the laser focus is stable in its prealigned position without any drift. This is a prerequisite for precise laser micromanipulations with highest possible accuracy in all day use.

PALM[®] products are well known for their precision and reliability. The PALM[®] MicroLaser Systems are deployed in a wide array of research, biological and industrial applications. The one-of-a-kind laser technology makes it possible for microscopic specimens to be captured, positioned and microsurgically processed with absolute precision. Unlike other systems, there is no risk of contamination due to our patented LPC (Laser Pressure Catapulting) process, lifting the desired objects into a collecting vessel for further analysis only by the force of laser light.

The systems are supplied as turnkey installations and characterized by a long service life and easy operation. PALM[®] MicroLaser Systems require the space of a normal desk and just need common power supply. As a matter of course, the systems comply with international safety requirements.

The company has adopted a quality management system according to ISO 9001 and DIN EN 46001, and furthermore, the devices are accredited as medical products in the EU.

- **P.A.L.M. – A Specialist for the Support During Your Work**

P.A.L.M. offers technology hardware with an excellent, worldwide background. Not only technical service and training activities for the authorized P.A.L.M. dealers are available but also expert knowledge in a broad range of scientific support. The potential of the P.A.L.M. technology is described in more than 400 published scientific papers.

The company runs a Service & Application Laboratory which was the first of its kind worldwide, providing expert resourced services. The P.A.L.M. specialists are ready to give individual and detailed advice whenever it is required. The interesting services range from RentalLab, where the customer can prepare his own samples with the aid of the qualified P.A.L.M. staff, to ScientificSupport in special questions with practical advice directly to the bench.

- **Samples and Disposables**

Any biological sample is suitable for the non-contact laser microdissection and the laser pressure catapulting. Up to now, there have been reported no ultimate restrictions regarding the origin of selected specimen or applied preparations and staining procedures. Even archived material can be catapulted from glass slides. For convenient procedures, most samples are mounted on membrane slides. This preserves morphology and thus enables automated routine processes.

For routine and automation, P.A.L.M. has developed a plenty of custom made disposables and improved a lot of routinely available laboratory equipments for the needs of routine microdissection.

- **Investment for the Future**

With the newly developed PALM[®] MicroBeam HT, the P.A.L.M. product family has been supplemented with a versatile and reliable tool, especially designed for high throughput screening needs in the pharmaceutical industry. The available technologies and handling protocols enable your organization to focus on things really deserving your attention and not get stuck in a lot of routine work. Especially the purity of the samples will lead to saving time and money, as you will be faced with clear results from the beginning of your work.

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Detailed information about microdissection and the appropriate equipment can be found on the homepage: <http://www.palm-microlaser.com>.