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Supplement to the Treatise

WOLFGANG RUNGE: TECHNOLOGY ENTREPRENEURSHIP

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Wolfgang Runge

Nanion Technologies GmbH

I also hope that the nomination of Nanion encourages also others to firm's foundation.
(Ich hoffe außerdem, dass die Nominierung von Nanion auch anderen Mut zur Gründung macht.
Niels Fertig, Co-founder of Nanion Technologies [Deutscher Gründerpreis]

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Nanion Technologies GmbH is a German private limited liability company (LLC, GmbH in German) founded in 2002 in Munich by three persons of whom Dr. Niels Fertig and Prof. Jan Behrends currently take to positions of the CEO or Chairman of the Board, respectively.

Nanion develops and markets instrumentation (patch clamp devices), related consumables (for instance, patch plates), and services for automated patch clamping. The *patch clamp technique* [Wikipedia-1] is widely used for the analysis of ion channels, which play an important role in many of the cells vital functions, especially in the cardiovascular and nervous system.

> The key aspect here is that Nanion Technologies has automated a previously largely manual time-consuming process by a high-throughput process.

It is a very lucid example of how a successful university research project was used to build a business which designs and manufactures research equipment for the academic and industrial research environment.

Nanion presents a complete cascade of a technological development:

“Based on the scientific results of academic research, a spin-off company was founded which quickly developed a versatile technology, resulting in customer-oriented products successful on the international market which led to the expansion of the company and the creation of high-value jobs. This development demonstrates the power of academic research in Germany and exemplifies comprehensively how pure basic research can breed technological innovation.” [CeNS 2007]

Nanion combines bio- and microtechnology in a company serving the life sciences industry by offering products and services which will dramatically increase the speed and efficiency of the drug discovery process in an important segment of the pharmaceutical market. Nanion bases its business on a proprietary chip technology and will design and develop High Throughput Screening (HTS) systems for ion channel active drugs (ICADs). Ion channels are prime targets for innovative medicines aimed at many important diseases.

Nanion is a success story of organic, cash flow-based company growth and dedicated young professionals.

The Market and Technology

Ion channels play an important role in numerous cell types and occur as large families of related genes with cell-specific expression patterns. They are proteins which can generate a pore in the cell membrane and can open and close and thus allow ions to enter or leave the cell.

Ion channels may be opened and blocked by active chemical substances. Therefore, they represent ideal targets for pharmacological substances (drugs).

Tissue specific distributions of ion channels will play a much more important role as therapeutic drug targets in the future and, therefore, make ion channels a favorable class of selective, tissue specific drug targets. Ca. 30 percent of all disease are affected directly or indirectly by ion channels. Currently, there are active pharmaceutical research and development programs involving ion channels in a number of areas, including asthma, inflammation, arrhythmia and central nervous system (CNS) disorders. Among the prominent examples the groups related to dysfunctional ion channels are cardiac arrhythmias, diabetes, hypertension, angina pectoris and epilepsy.

Already today drugs targeting ion channels are estimated to generate over $6 billion in sales per annum. But, in spite of their remarkable physiological value, ion channels have stayed a relatively unexploited therapeutic target class. Major challenges for high throughput screening (HTS) with high information content have been the main limiting factors for an explosion of R&D of the subject.

There are two general directions:

- First, find new ion channel active drugs and
- Second, test drugs concerning side-effects on ion channels.

Estimates for the ion channel screening market have placed a value estimated in 2004 to be $58.9 million (ca. €49 mio.) and $15.7 million for use in-house and outsourced profiling, respectively.

“The market for patch clamp/ion channel screening is very dynamically growing,” said Fertig. “This is mainly due to the new enabling technology of automated patch clamp systems. Planar patch clamping really has revolutionized the way ion channel screening is carried out in the industry. Since its advent, the interest in ion channels as drug targets has tremendously increased,” he added [Outsourcing-Pharma.com 2005].

Ion channel technologies increased considerable in importance as an *enabling technology* for drug discovery. The total worlds market for nano-enabled drug discovery was estimated at $121.9 million in 2004. For 2004-2012 the market was forecasted to grow at a compound annual growth rate (CAGR) of 29.3 percent, to $955 million at 2012. The lab-on-a-chip (LOC) devices and microfluidics market was projected to generate sales of $1,530 million in 2012 [Business Insights 2005].

The firm D&MD (Drug & Market Development) estimated the market for ion channel tools to reach one billion dollars in 2006 [BioPro 2004].

According to a report by NanoMarkets from 2005 [NanoMarkets 2005; Needham 2007] nano-enabled drug discovery solutions would generate revenues of $1.3 billion in 2009 and grow to $2.5 billion in 2012. The firm projected that labs-on-a-chip and arrays would offer the largest opportunities with nanoparticulate-based solutions also showing significant growth.

NanoMarkets said that the impact of nano-enabled drug discovery is expected to be both broad and deep, affecting numerous areas of the drug discovery process. The report predicted that by 2009 19 percent of nano- enabled drug discovery revenues will come from the control and analysis of cells, while another 13 percent will come from DNA/RNA sizing, electrophoresis and quantitation. Genotyping will account for another 11 percent of revenues and high-throughput screening will take another 10 percent.

In this context electrophysiology comprising the study of the electrical properties of biological cells and tissues plays an important role. It involves measurements of voltage change or electric current on a wide variety of scales from single ion channel proteins to whole organs like the heart (Wikipedia). In particular, it is the cardiology specialty that diagnoses and treats heart arrhythmias, or problems related to the heart's electrical system.

In 2008 significant demand existed in pharma and biotechnology to access *ion channel testing services* and this was reflected by the number and the variety of service offerings. The majority of GLP (glucagon-like peptide) cardiac safety hERG testing that day was outsourced *using manual patch clamping*. According to Wikipedia hERG (the human Ether-à-go-go-Related Gene) is a gene (KCNH2) that codes for a protein known as Kv11.1 potassium ion channel. This ion channel (sometimes simply denoted as 'hERG') is best known for its contribution to the electrical activity of the heart that coordinates the heart's beating

At that time automating patch clamping (APC) systems was undertaking an ever increasing role in the services offered and there was increasing acceptance of their use as alternatives to the “gold standard” manual patch clamp. This was due to improvements in quality of data generated with APC systems and the significant wealth of experience gained in their use. In the highly competitive area of cardiac safety hERG testing *price and turn-around time* are key factors in the selection of a fee-for-service provider [Comley 2008].

The *major issues with automated patch clamp* in 2010 are described by Clare [2010]. Instruments are a considerable investment although novel instruments with reduced costs were on the horizon. But, *running costs*, especially for the consumables (for instance, patch plates), can be prohibitive especially for more sizeable screening projects. These are expensive to fabricate since they have to be precision made, with high levels of quality control, because achieving tight electrical seals across the whole plate (or seal chip) is crucial for the overall efficiency of the process. Improved efficiencies in production of these consumables, and therefore reduced costs, would have certainly helped broaden the future application of these technologies across the drug discovery industry.

A recent market research report on “ion channel screening trends” [HTStec Limited 2011] pointed out, for instance, that

- The class of ion channels of most interest to respondents was voltage-gated sodium channels.
- Of the ion channel activities undertaken in house most respondents were carrying out screening of lead compounds against specific ion channel targets.
- 61 of 133 validated respondent labs were planning to purchase a total of 104 new APC systems over the next few years.
- The automated patch clamp (APC) systems respondents expressed greatest interest in purchasing over the next few years were MDC Ionworks Barracuda and Sophion QPatch HT/HTX.
- Most respondents expect a turnaround of 2 weeks when outsourcing most ion channel assay types.

- Respondents prefer to run in house the majority of their ion channel testing activities, apart from safety assessment (compliant) assays which they mainly outsource.
- Data quality most influences a decision to select an outsourcing partner for ion channel testing.

The median 2011 annual budgets for ion channel testing were: $50K-$100K for in house consumables; $25K-$50K for CAPEX (capital expenditures) purchases (instruments); and $5K-$10K for outsourced testing at fee-for-service providers.

The total market in 2011 was estimated to $110 million for in house consumables, the biggest proportion of which was spent on APC patch plates; $144 million for CAPEX purchases (instruments); and $121 million for outsourced testing at fee-for-service providers [HTStec Limited 2011].

Nanion Technology has given a strong impetus for the development of the market. By 2011 it estimated the market for patch clamp devices as given in Table 1 [Fertig 2012].

Table 1: Market segments and market values [Fertig 2012].

	Pharma	**Biotechs**	**Service Providers**	**Research Institutes**	**TOTAL**
Number of Customers	300	500	50	10.000	ca. 10.000
Sales Potential per Year	€100 mio.	€50 mio.	€20 mio.	€75 mio.	ca. €250 mio.

The patch clamp method was developed by the Germans Erwin Neher und Bert Sackmann who were rewarded for their works by the 1991 Nobel Prize in Physiology or Medicine. [1] The patch clamp technique soon became an essential tool for scientists studying the activity and behaviour of a host of ion channels in many types of cell, and also for understanding how defective regulation of ion channels underlie a host of diseases.

With the manual method a scientist/researcher (!) can investigate approximately 10 cells per day. With Nanion's newest product a specially trained person (a skilled employee; in German Fachkraft) may generate 5,000 data sets per day.

The Entrepreneur(s)

Dr. Niels Fertig is a co-founder of Nanion and was the essential driver of the firm's foundation and its development.

Niels Fertig (born1972) has a personality who "is attracted by application" of research. After his "social service" (an alternative to serving in the German army) at the hospital of the University of Göttingen (Germany) he started to study *physics* at that university though his *primary goal was a study of medicine*. But he thought physics to be more profound [Mayerl 2010].

During a one year study at the University of California at San Diego he was engaged in artificial neural networks, mathematical models or computational models that are inspired by networks or circuits of biological neurons. That led to contacts to electrophysiology and then to a diploma and doctoral thesis at the Ludwig Maximilian's University of Munich (LMU) [Mayerl 2010].

The stay in the US shaped Niels Fertig's personality by private experiences, but also concerning the American university life and participating in the day-to-day way of studying. He was attracted by the fact that compared to Germany research and teaching has a stronger emphasis on practice. Furthermore, professors are more and easier accessible by undergraduates and open to cooperation with students [Loitz 2003].

Niels Fertig finalized his study of physics at LMU with a doctoral degree assessed by the highest honor ("summa cum laude"). In the same year he founded with two partners Nanion Technologies

GmbH [Fuchs 2005] he and explained why he did not pursued an academic career, but rather to become an entrepreneur as follows [CeNS 2007]:

“During my research as a Diploma and then PhD student, I worked on the development of a microstructured chip for the patch-clamp technique. The initial goal of the chip-technology was to improve the resolution of the measurement compared with the results obtainable with the common patch pipette. In the course of this research and by presenting the results at international conferences we soon became aware of the high potential for application of our investigations.

Personally, I am highly attracted by the combination of scientific and entrepreneurial activities. Therefore, I realized quite early during my PhD that I wanted to found a company and make this technology accessible to others. Academic research attracts me a lot, but I really enjoy bringing scientific results to application and receiving the feedback of the customers.

In my case, I can hardly imagine a profession more exciting than building up one’s own company and that’s the reason why I am more than happy to discuss with potential founders about their plans and to share experiences at any time.”

And he explained: “I never strived for a permanent job in a large industry firm due to long routes to decisions and the often reduced position for own decision-making and initiative. For the alternative of an academic career for young researchers the very long road to a secure perspective and the relatively low compensation are deterrent. I prefer my current activities. Doing things myself is a big challenge and very motivating challenge.” [Loitz 2003]

While doing his doctoral thesis Niels Fertig demonstrated “a tolerance for frustration, staying power, inspiration, and transpiration.” [Deutscher Zukunftspreis 2007] Mayerl [2010] has characterized Niels Fertig to have tenacious perseverance which gives momentum to the whole firm when at the end of a talk he said. “We shall continue to grow. We drive the field before us.”

According to his self-assessment Niels Fertig views *perseverance (sticking to a belief or idea) and ambition* as his important traits. "It is crucial that you have perseverance, faith in yourself and in the subject and also cushion and motivate each other. Because everyone has sometime a bad patch.” (“Entscheidend ist, dass man Durchhaltevermögen hat, an sich und an die Sache glaubt und sich auch gegenseitig auffängt und motiviert. Denn jeder hat mal irgendwann einen Durchhänger.”)[DZP07].

His conviction relates to “Inspired by Science. “Growing from strong scientific roots.” “In this way, … innovation results from a combination of intensive research, applied methodology, an unprecedented power of observation and, not least, a great passion.” {Nanion Technologies 2010a}

And after five years of developing a new technology venture Niels Fertig summarized the past and the future as follows:

“We firmly believe that Nanion will remain a leading provider of automated electrophysiology systems and expand its market presence. We hope that Nanion keeps developing as in recent years, growing and still will have happy customers. Important addition to all successes: in five years we still want to have fun with Nanion!” (Wir glauben fest daran, dass Nanion ein führender Anbieter von automatisierten Elektrophysiologiesystemen bleiben und seine Marktpräsenz weiter ausbauen wird. Wir hoffen natürlich, das Nanion sich so weiter entwickelt wie in den letzten Jahren, wächst und weiterhin glückliche Kunden hat. Wichtig neben allem Erfolg: wir wollen auch in fünf Jahren noch Spass mit Nanion haben!) [Interview Blog 2007]

As a founder you just have to also overcome some hurdles. If you cannot push through, for you perhaps being a businessperson is not quite right. (“Als Gründer muss man eben gewisse Hürden auch nehmen. Wenn man sich da nicht durchsetzen kann, ist vielleicht Unternehmer nicht ganz das Richtige.”) [Mayernl 2010]

Finally Fertig is quite aware that success often depends on luck; but luck is needed also (“Naturgemäss hängt beim Erfolg auch vieles vom Glück ab, aber das braucht man eben auch.” [Interview Blog 2007]

Development of the chip-based patch-clamp technology began in 1998 at the Center for Nanoscience (CeNS) at the University of Munich (LMU) where Niels Fertig, Robert H. Blick (a physicist) and Jan C. Behrends (a physiologist) elaborated the basis.

Soon after the Nanion formation Jan Behrends became Professor of Physiology at the University of Freiburg (Germany) and Prof. Dr. Blick took Professorship in Solid-State Physics in Madison, Wisconsin, USA, respectively. But both continued to advise Nanion and remained partners (in German Gesellschafter) in the LLC (GmbH).

In addition to his function as Chairman of the Advisory Board of Nanion, Dr. Behrends continued to cooperate academically with Nanion Technologies on joint development projects for secondary technologies [Deutscher Zukunftspreis 2007].

According to his Web site and DZP07 [2007], Jan C. Behrends studied medicine at the University of Munich, Germany, spending a year as a Research Student at the Department of Physiology of Kyushu University, Japan.

From 1992 to 1994 he was an INSERM fellow at the Institut Pasteur, Paris, France and from 1994 to 1995 a fellow of the German Research Council (DFG) at the Max-Planck Institute for Psychiatry in Martinsried near Munich. He then returned to the University of Munich as Research Associate and Assistant Professor (1997), obtained his Habilitation in Physiology in 2002 and was appointed Professor of Physiology at the University of Freiburg in 2003.

His research focuses on cellular and membrane electrophysiology including mechanisms of synaptic transmission as well as on the development of novel experimental tools for electrophysiology, biophysics and nanoscience, including automated higher-throughput patch-clamp and lipid bilayer recording systems.

Jan Behrends is an “entrepreneurial professor” identifying, mentoring and supporting entrepreneurial talent. In 2002, correspondingly he co-founded Nanion Technologies GmbH with Niels Fertig.

He is currently academic mentor of the start-up project Ionera in the Exist Technology Transfer Program of the German Federal Ministry of Economics (BMWi) which is in a pre-startup phase of a new technology venture.

The key entrepreneur here is Dr. Gerhard Baaken and the basis is his dissertation from 2008. This dissertation was done with the Institute of Microsystem Technology (Freiburger Institut für Mikrosystemtechnik – IMTEK) with Prof. Dr. Jürgen Rühe in cooperation with Prof. Behrends [BioPro 2013].

Ionera should be founded officially by autumn of 2013, but foundation as a GmbH (LLC) was in early 2014. It will provide a universal chip platform for ion-conductance based analytics. They develop and customize multi-electrode cavity array (MECA) chips, nanopore and channel protein reconstitution kits and assays. [2] While Ionera will be focused entirely on the production of the chips and the analysis kits, Nanion Technologies GmbH will make the appropriate instruments available [BioPro 2013]. The current focus (“ionera ... wherever ions flow”) is on n high-throughput bilayer electrophysiology and the MECA-16 chip.

Awards and Publicity

Nanion Technologies GmbH and its co-founder Niels Fertig are multiply awarded with many, also prestigious prizes in Germany [Nanion 2010a]. Additionally, these prizes provided some (minor) contributions to financing the startup.

2009:

Nanion received the German Founder's Award ("Deutschen Gründerpreis") as the winner in the category "Climber" as it succeeded in the transfer of scientific research results into products within five years and achieving breakeven after just two years.

The German Founder's Award is the most prestigious award for outstanding entrepreneurs in Germany and is distinguished by providing entrepreneurial role models in different business phases [Nanion Technologies 2009a].

In the same year Nanion got the STEP Award [STEP Award 2009; Infraserv 2009]. The award included a monetary component of €50,000 as well as consulting, services and goods valued €50,000 to support further growth, such as patent search, consulting concerning strategy and business development, search for cooperative partners and utilizing technical workshops.

2008:

Innovation Award of the German Economy; nominated 2008 [Nanion Technologies 2010a].

2007:

In 2007, Nanion reached the final round in the competition for the "Deutscher Zukunftspreis" (German Future Award, Federal President's Award for Technology and Innovation) nomination [CeNS 2007; DZP07 2007].

2006:

Nanion Technologies was rewarded with the Bavarian Innovation prize 2006 for providing technology for fast and automated testing of effects and side-effects of drugs by electrophysiological measurements with high-throughput screening focusing on ion channels [Bavarian Government 2006].

2005:

HanseNanoTec – the Competence Center for Nanotechnology in Hamburg (Germany) – awarded the "Nanoscience Prize 2005" to Niels Fertig for his excellent practice-oriented work [Fuchs 2005].

Also in 2005 during the "Business Day" of the Bavarian Credit Cooperatives ("Volksbanken und Raiffeisenbanken") Nanion Technologies GmbH received the innovation award "Medium-Sized Firm of the Year" which is worth €15,000 [FPMI 2005].

2003:

For his work "The Nano-Patch-Clamp Principle: Nanofabricated Glass Chips for High-Throughput Electrophysiology" Niels Fertig received the highest level "*iKuh-Award"* for application-oriented nanotechnology sponsored essentially by the IVG Business Park (near Munich, Germany) worth €5,000 [Rücker 2003; Loitz 2003].

In the context of business plan contests there were in 2001:

- Science4Life Award, winner concept phase, 2001
- Genius Biotech Award, Business Plan Competition, winner best technology, 2001
- start2grow Microtechnology Contest 2001, winner best business plan, 2001

The Business Idea, Opportunity and Foundation Process

The Pre-Start Phase and the Idea

Development of the chip-based patch-clamp technology began in 1998 at the Center for Nanoscience (CeNS) of the University of Munich (LMU) where Niels Fertig, Robert H. Blick (a physicist) and Jan C. Behrends (a physiologist) elaborated the basis. The idea for the chip emerged at an initiating conference and kick-off meeting for an interdisciplinary special research division for

nanotechnology and was later funded as a sub-project by the DFG (Deutsche Forschungsgemeinschaft, related to the National Science Foundation (NSF) in the US) [Deutscher Zukunftspreis 2007; Editorial 2007].

Researchers in *special research areas* funded by the DFG ("Sonderforschungsbereiche" – SFB, Collaborative Research Centres) are also encouraged to collaborate with industrial partners. Usually, in all these types of cooperation the emphasis is on *pre-commercial (pre-competitive)* activities.

Within the scope of his diploma and doctorate work, Niels Fertig together with Dr. Behrends and Dr. Blick, his academic advisors and heads of the SFB subproject, developed the principles of the planar patch-clamp method.

In 1997 almost no-one believed that the patch clamp method can be automated. But this is exactly what has been achieved. In his dissertation Niels Fertig together with his academic advisers developed an innovative approach: Development of the related "*patch-clamp-on-a-chip" technology* which allows patch-clamp measurements without micro-manipulation or visual control.

This is *an outstanding simplification and improvement of the classic method*. Using state-of-the-art micro-structuring methods, Nanion Technologies produced planar chip substrates made of borosilicate glass, containing perforations of only one micrometer (1 millionth of a meter). These *biochips replace the glass micropipettes* generally used for patch clamp rechanneling [Deutscher Zukunftspreis 2007; Editorial 2007; Adam 2009].

While the classical patch-clamp technique is the gold standard for ion channel investigations, it is *labor-intensive and requires (highly paid) skilled scientists*. It has one serious drawback: For patch clamping a skilled experimenter has to micromanipulate a glass micropipette under microscopic control in order to be able to record from only one cell at a time.

The placement of the pipette requires very high skill. In a complicated process, it must be maneuvered to the test object using a sensitive adjusting apparatus. The *sample throughput is correspondingly low*: On a good day, a research scientist can study around ten cells using this method. This naturally does not meet the demands of drug development. It fails to meet, for instance, demands of *pharmaceutical drug testing with regard to cost and time necessary per data point* [Adam 2009; Deutscher Zukunftspreis 2007].

For developing new active pharmaceutical ingredients (APIs) and drugs the pharmaceutical industry requires data-rich measurements with

- high throughput and
- high information content.

A corresponding automated patch clamp for high throughput screening (HTS) was highly in demand in drug research targeting ion channels since in a short period of time it can test the effects of a variety of substances that may possibly have an impact ion channels.

> For the APC situation *the experimental arrangement is reversed*: Instead of moving the pipette to the cell, the cell is now positioned on the aperture in the chip using a negative-pressure suspension. Due to vacuum pressure single cells are sucked directly over the hole and are positioned optimally quickly. This new technology, automated and parallel patch-clamp recording, creates the basic conditions for *standardized and industrial use* (Figure 1).
>
> Each aperture may get a different cell and allows other pharmaceutical active substances to be tested. According to Dr. Fertig "the measurements are of high quality as many parameters can be controlled in parallel. Simultaneously the automated process increases the throughput." [Deutscher Zukunftspreis 2007; Adam 2009]

Nanion provides an automated process that is *high-quality* also in the sense that for drug research with the methods one can say with great certainty whether a substance acts or interacts with given target structures – contrary to, for instance, optical measurements.

And there was an additional favorable circumstance for Nanion – regulation. Its technology is useful not only to test whether a drug exhibits a potentially positive effect via a relevant ion channel. It also can be used to inquire into negative effects, side-effects of promising drugs. In the US (here the Food and Drug Administration, FDA) and EU medicaments require to pass certain health-related test and get permits by the related registration offices before they get approval to enter the market.

So far, many investigations concerning side-effects of drugs were performed using animals during a later stage of developing a drug. But Nanion's technology for ion channels allows tests concerning side-effects for many illnesses already during an early phase of drug development. The drug candidates with dangerous side-effects can be taken out of the development chain und thus can save a lot of money. It is a further driver for demanding related ion channel measuring technology.

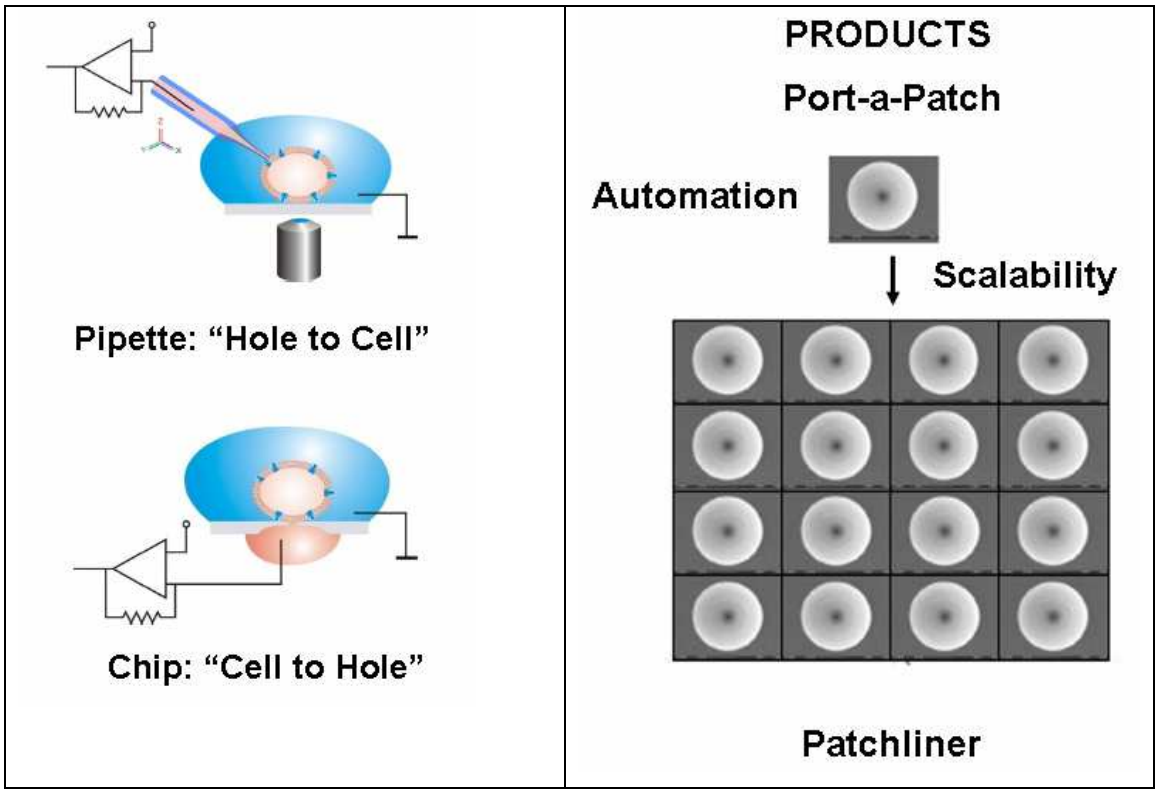

Figure 1: Nanion Technologies' Products: Process automation (left) and scalability (right) [Fertig 2012:13,14].

Based on the scientific results and the related business idea Niels Fertig, Robert H. Blick and Jan C. Behrends founded Nanion Technologies GmbH in January 2002 with two employees [Fertig 2012]. The foundation may have occurred with a sense of urgency as in 2000/2001 "patch clamp startups" emerged and Axon Instruments, Inc. already was working on automated patch clamp (APC) systems (cf. Competition).

The trio presented in 2002 the first chip-based patch-clamp measurements in the Biophysical Journal (Fertig, N., R.H. Blick, and J.C. Behrends, "Whole cell patch clamp recording performed on a planar glass chip", Biophys. J. 82(6): 3056-3062 (2002)). Nanion was already half a year old when the paper was published [Mayerl 2010].

In particular, Fertig pushed the planning of a firm's foundation through spin-out. The three scientists participated in a business plan contest and developed a concept for commercial exploitation of the technology [Editorial 2007; Deutscher Zukunftspreis 2007]. Fertig considered the par-

ticipation in the Munich business plan contest to be very helpful to get professional feedback and to establish contacts [Interview Blog 2007]. In 2001 he earned a third position in the “business plan contest for microsystems technology” (“start2grow”) in the German State of Northrhine-Westphalia [Fertig].

The results presented at specialized congresses and conventions as well as in particular the initial publication caused quite a sensation and met with enthusiasm internationally. And Fertig, Blick und Behrends very soon became aware of the full commercial potential of the planar patch-clamp technology – in addition to the academic interest in the work.

Correspondingly, future customers could be envisioned in industrial and academic/research environments.

After foundation Nanion presented the first prototype of a patch-clamp automation during the Annual Meeting of the American Biophysical Society in March 2003 [Editorial 2007]. Launch of the *first product* (Port-a-Patch©, Figure 1) was in the third quarter of 2003 [Adam 2009]. When Nanion started in January 2002 it had merely two employees, which have increased about tenfold within five years [Nanion Technologies 2007b].

A single channel automated patch clamp device, the NPC©-1 Port-a-Patch©, was the first of Nanion’s products and was successfully launched in 2003 (Figure 1).

For the firm laboratory and office space was originally leased on the top floor of the Physiological Institute of the University of Munich (LMU), which made it possible to utilize the existing infrastructure. Ultimately, in the early phase, the meager means available had to be used as efficiently as possible [Deutscher Zukunftspreis 2007].

At the time when Nanion was founded in the German Federal State of Bavaria there was a public program called “Flügge” ("Förderprogramm zum leichteren Übergang in eine Existenzgründung") to support spin-outs from universities during the seed- or the startup phase. Furthermore, Nanion Technologies got also support for development projects, for example, by the Federal Ministry for Education and Research (BMFB), in order to be able to undertake the ambitious research work with the necessary resources [Deutscher Zukunftspreis 2007].

In particular, during conceptualization of the startup the Flügge-Program supported young scientists with scholarships for one or two years corresponding to a half-time job at the university [LMU]. During the early phase of Nanion Niels Fertig and Michael George participated in the Flügge-Program [CeNS 2008].

The Team

Soon after the Nanion formation, Prof. Dr. Behrends and Prof. Dr. Blick took professorships in Physiology in Freiburg and Solid-State Physics in Madison, Wisconsin, USA, respectively, but they continued to advise the company. In addition to his function as chairman of the Advisory Board, Dr. Behrends continued to cooperate academically with Nanion Technologies on joint development projects for secondary technologies [Deutscher Zukunftspreis 2007].

During the founding year biophysicist Dr. Michael George was the first employee of Nanion [LMU 2008] who since then filled the important function of manager of technical development (now CTO).

Then the *leadership team* of Nanion was built up carefully based upon need.

In March 2003, electrophysiologist Dr. Andrea Brüggemann joined the company as a partner. With years of experience in electrophysiology and the development of ion channel active drugs she *met the requirements crucial to development work* at Nanion Technologies [DZP07 2007]. Thus, the management team at Nanion Technologies was almost complete with Dr. Fertig (CEO), Dr. George (CTO), Dr. Brüggemann (CSO). Dr. George joined also as co-owner in February 2007 [Deutscher Zukunftspreis 2007].

Actually, Andrea Brüggemann got to know Niels and Michael George at a conference – the “chemistry” was immediately right. After leaving her previous employer, the pharma giant Aventis,

she went to Nanion and all realized that she actually would be the missing piece of the puzzle for the company: She had four years of experience working on the other side – the (anticipated) customers of Nanion's devices. She knows what the customer wants [DZP07].

Later, according to entries in the Firmenwissen Database (July 7, 2009) share capital (in German Stammkapital) of the GmbH/LLC was €60,600. Partners included

- Managing Directors: Niels Fertig (€20,000), Andrea Brüggemann (€9,100)
- Co-Founders: Jan Behrends (€10,000), Robert Blick (€5,000)
- Michael George (€5,900)
- BioM AG Munich BioTech Development (€9,100) – a public investment firm
- Three other partners with each contributing €5,000.

To strengthen research, product development as well as marketing and sales activities Nanion hired Dr. Cecilia Farre in 2006 (now Marketing Director and Senior Scientist of the leadership team; cf. Organization). She graduated in analytical chemistry and electrophysiology from Gothenburg University, Sweden, where she also held a postdoctoral position in electrophysiology. Dr. Farre was employed as project manager and later on Vice President of Key Projects at Cellectricon AB, Gothenburg, Sweden, where she played a key role in the development and commercialization of the company's microfluidics platform [Nanion Technologies 2006].

Niels Fertig explained the rational as follows: "We have successfully introduced our entry level device for automated patch clamp, the Port-a-Patch, which has been very well received by our customers. With the upcoming launch of our robotic multi-channel patch clamp workstation, the NPC-16, we want to strengthen our R&D team for customer support as well as our M&S for both the Port-a-Patch and the NPC-16. Dr. Cecilia Farre, with her strong background in ion channel screening instrumentation and commercialization, is a perfect fit to fill this position and we all welcome her on board!" [Nanion Technologies 2006]

Financing and Pursuit of Other Resources

Niels Fertig appreciates his independence from financial backers who talk and interfere into anything. And according to Michael George

> "We don't look for investors as we can *finance development of new products from our cash flow*. Additionally, our technology reduces the cost of research. Moreover, demand increases as agencies which approve drugs require particular measurements of ion channels." [LMU 2008; Deutscher-Gründerpreis 2009] (Emphasis added)

Niels Fertig values also *networking* as an important resource for entrepreneurship. In particular, the Munich area with two universities and a university of applied sciences was seen to provide good opportunities for cooperation. Furthermore, as the *founders and some of the first employees originated in the Center for NanoScience of the LMU* they provided a natural network of the academic environment. In particular, during the first years Nanion was located in the university [Interview Blog 2007].

Initial financing of Nanion was through a seed investment of BioM AG of Munich and an investment of the tbg of Bonn run as a "silent partnership" [Runge:ch. 1.2.7.1] (tbg –Technologie Beteiligungsgesellschaft des Bundes – is an investment organization of the German Federal Government and now part of the public KfW Group) [Deutscher Zukunftspreis 2007; CeNS 2008].

According to the German official legal document "Elekronischer Bundesanzeiger" (Electronic Federal Announcements) the silent partnership was later canceled and the investment capital (€85,000) was paid back by Nanion on August 10, 2006. A related additional fee of €10,500 was paid by Nanion in 2007.

BioM AG was set up by the Bavarian Government as a service, consulting and investment organization targeting at development of the "Biotech Region Munich" to become a leading biotechnology center in Europe [Bavarian Government 2006]. In 2009 BioM sold its stake in Nanion Technologies [Bavarian Government 2008].

According to Adam [2009] Nanion's starting capital amounted to €500,000.

In 2009 a management-buyout (MBO) of Nanion by its management occurred [Fertig 2012].

Nanion's development exhibits *goal persistence* [Runge:p. 675-676, Figure I.122] – towards building a large robot.

Economically, the foundation year 2002 of Nanion was not favorable. According to Fertig, "After the burst of the Internet bubble we were one of the last firms which got money." There was a seed financing of BioM and that was all. A second financing round planned for 2003 did not materialize due to the poor investment climate.

The original plans to build a large robot for testing simultaneously sixteen cell samples had to be postponed. "We then have built a small device which could only test a single sample, as this was feasible for us." The mini-robot became a big success, "it was literally torn out of our hands." [Adam 2009]

And *Nanion became profitable after just two years in 2004*. By September 2004 Nanion had seven employees [ENNaB 2004].

For Fertig, in retrospect, this period of quite tight money had some positive features. He explains, "In hindsight, this extremely scarce funding had a positive impact, because we had to focus on the essentials." We have learned how important it is to orient oneself toward the market and not toward the investors." ("Dabei haben wir gelernt, wie wichtig es ist, sich am Markt zu orientieren und nicht an den Investoren"; "Der Markt ist das Ziel, nicht die nächste Finanzierungsrunde.") [Interview Blog 2007; Deutscher Zukunftspreis 2007; Adam 2009].

We have established the firm in 2002 at a time when investors were very cautious and did not make early-stage financings. Back then we could win BioM as an investor, but got only a fairly small amount. Therefore, we were at the outset focused on an efficient utilization of financial means, followed the market early and launched our first product already in 2003. [Interview Blog 2007]

Nanion was very conservative from the start and used its resources very efficiently and restrained. When developments were planned they asked themselves: Can we afford this, how do we do that? Often you get very simple, very good solutions you might not have taken into consideration if more money would be available {DZP07}.

The whole team was practicing modesty and focused on the development of next generation devices [Adam 2009]. The Nanion team was always *very careful to efficiently use available resources to fit market demand*, so that it could launch the first product (Port-a-Patch©) in the third quarter of 2003. Port-a-Patch was extremely well received in the pharmaceutical industry, in life science companies as well as in academic circles and Nanion achieved profitability in 2004. Since then Nanion is *profitable* and proceeds with *organic growth* [Interview Blog 2007; Deutscher Zukunftspreis 2007].

> The key learning of Niels Fertig, which he also recommends to all startups, was the requirement of *early contacts to customers* ("Der frühe Kontakt mit den Kunden habe dem Unternehmen gutgetan"). In his particular situation that meant, "Many customers want to try first on a small scale before they order the big robots." [Mayerl 2010]

Financing R&D by Publicly Funded Projects

What Nanion was and is doing continuously, is the third-party funding. For projects in which the firm enters "uncharted territory", it tries to acquire appropriate project funding [DZP07].

For further research and development of patch clamping in its early phase Nanion took advantage from grants and participation in projects funded by the Federal Government of Germany. For instance, Nanion was successful with the so-called Bio-ChancePLUS call for proposals of the German Federal Ministry of Education and Research (BMBF) to lead a "Verbundprojekt" ("joint project"; [Runge 2006:p. 162]) with the German firms conoGenetix biosciences und Evotec AG to further automate the chip-based patch clamp method. The whole project was valued €2 million

[BioM 2004]. conoGenetix biosciences GmbH (also funded by BioM) is a biotech company focused at that time on the discovery and development of natural peptidic ion channel modulators as drug leads for the treatment of neurological and autoimmune diseases.

On the other hand, Nanion participated in a project of the University of Munich (LMU) entitled "Nanostructured Interfaces for electro-mechanical addressing ion channel proteins" ("Nanostrukturierte Schnittstelle zur elektromechanischen Adressierung von Ionenkanal-Proteinen (code FZK: 13N8363)) funded by the BMBF [TechPortal] through running a sub-project "Manufacturing of chip-based apertures for measuring ion channel" ("Herstellung von chip-basierten Aperturen zu Ionenkanalmessungen"; project codes 13N8363-64 and FZK 13N8364) [Fertig 2007]. The project funding was awarded as non-repayable grants for the period March 1, 2003 till February 28, 2006 and amounted to €189,085. There was also funding of ca. €88.000 by the BMWi [AiF 2013]/

Though not big amounts also the money associated with the many prizes and awards Nanion received was helpful.

During this period Nanion entered the market fast with its first product, the single channel automated patch clamp device, the NPC©-1 Port-a-Patch© and established distributors for important markets in North America, Japan and China. Roughly two thirds of the customers are from industry, one third from the academic environment [LMU 2008]. Indusrial customers were mainly from pharma and biotechnology [Editorial 2007].

Technical development focused also on accessories and components for automated patch clamping. For instance, perfusion (in German Durchströmung) was optimized for small volumes and rapid fluid exchange. For this reason Nanion established cooperation with German ibidi GmbH. According to Wikipedia perfusion is the process of nutritive delivery of arterial blood to a capillary bed in the biological tissue. The development alliance aimed at a pump system by which cells suspended in a medium can be pumped circularly with minimal mechanical stress. Mechanical stress shall be largely reduced to prevent the unwanted cell activation [Bionity 2005].

Furthermore, Nanion together with the Institute of Applied Physics of the LMU ran a project funded via the PRO INNO program of the German Federal Ministry of Economics (BMWi) in the period 03/2004–06/2006 entitled "Automated adhesion construct with single molecule resolution of cells and cell membranes" ("Automatisierte Adhäsionsanlage mit Einzelmolekülauflösung an Zellen und Zellmembranen") by combining fluorescence-optical and scanning probe analytics and patch clamp technology involving its product Patchliner. Nanion developed the biochip for single cell positioning with microfluid perfusion as well as an electrophysiological-mechanical control of the cell [AiF 2007]

The Port-a-Patch© is a complete patch clamp setup with minimum foot print and very low maintenance requirements. Experiments are performed on a single cell at a time, whereby whole dose response curves can be obtained from a single cell. Due to its miniaturization, compound consumption is extremely low (in the µl range). The Port-a-Patch© enables a fast fluid exchange on the chip, allowing for experiments not only on voltage gated, but also on ligand gated ion channels.

Nanion achieved outstanding ranking for the overall instrument performance in a ion channel survey by HTStec focused on real user experience of automated patch clamping ("HTStec Ion Channel Trends 2005"). One of the key outcomes of the survey was the overwhelming success of Nanions Port-a-Patch: more than 80 percent of the Port-a-Patch users were very happy with overall instrument performance! This was by far the best rank compared to other instrument providers [HTStec Limited 2005].

A recent review assesses the Port-a-Patch and its further developments [Innovaro] in terms of utility, performance and accessories (Emphases added):

"The Port-a-Patch *replaces the conventional patch clamp rig* thereby offering the following advantages: *equipment up and running within a day*, *ease of use even for non-electrophysiologists*, extremely small footprint, insensitive to vibration enabling *very stable recordings*, small volume consumption, *also applicable for lipid bilayer recordings*.

The use of the Port-a-Patch *can be learned within a couple of days*, making it very suitable also *for educational purposes*. For the NPC-16 liquid handling cell application as well as the definition of experimental protocols are fully automated. The *throughput* is increased by a factor of ten for the NPC-16s and by a factor of 100 for the NPC-16p.

Nanion's NPC-1 Perfusion Chamber provides a fast and continuous perfusion. It allows accurate application of up to eight different compounds and solutions. The timing of the solution exchange can be controlled via the patch clamp software. PatchMaster by HEKA can be used to control the perfusion system without an additional interface."

More references to assessments of Nanion's products are given by Fertig [2012:29].

In 2006 Nanion introduced a second generation instrumentation, the Patchliner (Figure 1), for high quality electrophysiology with higher throughput (it is available now with 2, 4 or 8 simultaneous recording channels) as well as extending Nanion's microchip technology for applications in bilayer recordings.

Hence, automated patch clamp had become a reality over the last five years with Nanion certainly playing a vital role [Nanion Technologies 2007b]. And the chip-based platform offers extension by combining patch clamp experiments with other biophysical methods [Fertig 2007].

"The Patchliner is a robotic multi-channel patch clamp workstation for high quality cellular electrophysiology with increased throughput capabilities. High success rates in gigaseal formation and stable whole cell recording of 60-80 percent are routinely achieved. The Patchliner builds on the success of the Port-a-Patch technology, offering vast experimental flexibility with high quality and increased throughput." [Innovaro] [3]

For the firm's *development strategy* Nanion can rely on lots of ideas. The issue seen by Nanion's leaders was to find out what is relevant and which is best to cope with the existing employees and resources. Hiring just two new employees does not make sense for the leaders. It appears easier to implement projects that rely on available competencies, and then to grow with them [DZP07].

After the first growth phase and in response to its growth, after early years in the top floor of the Physiological Institute of the University of Munich (LMU), in 2006 Nanion moved into its own facilities, an old industrial loft at the center of Munich [Editorial 2007; Zelltim 2008].

The actual business idea and the foundation and early stage of Nanion is much more complicated, but lucidly and (like a diary) illustratively described in detail in DZP07 [2007] (*Fragen an die Nominierten – Questions to the nominees*).

> Originally it was not intention, to make a product of screening technology for the development of drugs. The original idea was to develop a better, even higher resolution measurement method for ion channels based on the small micro-and nanostructures Dr. Blick had developed. They wanted to develop a new, high-resolution method for measuring individual ion channels in order to spectroscopically measure small conformational changes which is small movements in proteins.
>
> They started with semiconductors, but found that these are not appropriate for the targeted microstructuring. Instead, they found that glass is ideal – as is used for pipettes of the patch clamp method. The subsequent development was not the application, but a scientific development. And Niels Fertig realized that it is fun to work on things that can possibly go into an application.
>
> After two years of development the group became aware that apart from scientific application there was the aspect of developing drugs and that they were not the only ones who develop this direction. Internationally, there were three or four groups that were working on it, and companies that promoted the development direction massively (Table 4).
>
> What was clear to all was that technologies have a certain time horizon (*Window of Opportunity*) within which they can enter the market, and they were also aware that they had

to *go ahead with it very quickly*. Hence, the pressure initiated activities for creating a spin-out and learning about business plans.

It is a major undertaking to write a business plan. The to-be founders invested a lot of time, but in exchange gained a lot of contacts with relevant persons, are they patent attorneys or tax consultants, or lawyers. The rationale to concentrate on business plans was to catch venture capital [DZP07]

But, in the end, “what we have written into the business plan were just finger exercises, much has not been realized." (Und das, was wir in den Business-Plan hineingeschrieben haben, das waren eher Fingerübungen, vieles ist nicht realisiert worden.”)

Due to financing problems after the Dot-Com Recession original plans to build a “big robot” had to be changed. One of Nanion’s advisors suggested starting just small, with developing at first a one channel device. And exactly that turned out to be a “cash cow.” One third of the customers during the early phase were universities and another third comprised small biotech firms. Contacts with the universities were extremely valuable as they provided much feedback for further developing the product.

The firm’s constellation was based on academics and technologists. There were no people from business administration or law; this usually puzzles investors. The advantage: all Nanion employees have a good understanding what the customers wants. They can quickly assess whether a customer’s proposal is not only relevant but also feasible. People can also try this with some effort. All are generalists; everyone makes everything and can try out things.

Corporate Culture

Nanion’s corporate culture means essentially science, people, team, networking and personal contacts with customers [Nanion Technologies 2010a].

It has a very flat hierarchy; everyone must take responsibility [DZP07].

As the founders of Nanion as well as some of its first employees originated with the CeNS Nanion has an extensive network in the academic environment [Interview Blog 2007].

Nanion Technologies was founded in an academic and creative environment and uses *a strategic network of experience and knowledge* as a strong basis for developing exceptional products [Nanion Technologies 2010a] It started as a an internationally operating multi-disciplinary RBSU (research-based startup) and continued as a *science-based NTBF* (new technology-based firm) with ca. 60 percent of its workforce being scientific/research employees and most of them with a doctoral degree [Adam 2009] (cf. Key Metrics).

Experience is seen as the best teacher – which implies sharing of information, knowledge and experience among employees.

“Inspired by scientists” is the definitive essence which provides the basis of all Nanion products. The focus is on people – scientists not science! Follow a combination of intensive research, applied methodology, the power of observation and, not least, a great passion. For Nanion development means more: Scientists work together with engineers and designers [Nanion Technologies 2010a]. The focus on science implicitly means an attitude and performing “continuous learning.”

In essence Nanion employs (bio)physicists, chemists, physicians and electrical engineers [Loitz 2003] as well as biologists, microsystem engineers, bio-engineers and people from mechatronics. According to Fertig, “They are all very critical for our success. It boils down to the expertise and dedication of everyone. (“Sie alle sind für unseren Erfolg sehr entscheidend. Auf die Kompetenz und Einsatzbereitschaft jedes Einzelnen kommt es an.”) [LMU 2008].

But additionally the leadership/management is crucial for such a startup: a multi-disciplinary firm has to work as an inter-disciplinary team towards the firm’s goals with everyone having internalized the importance and contribution of his/her role.

This is reflected by Fertig's conviction: You cannot set up a technology venture as a single person. Just as important as a good business idea is the well-fitting team, with which one can realize the idea ("Als einzelne Person kann man kein Unternehmen aufziehen. Genauso wichtig wie eine gute Geschäftsidee ist das passende Team, mit dem man die Idee realisieren kann.") [Loitz 2003].

Therefore, the overall effects and achievements of leadership and employees result from the "*Team Nanion*" [Fertg 2012:20].

Customer-orientation [Runge:p. 406] of *all employees* is at the center of efforts of all employees. Individual service and support is what Nanion calls superior customer care [Nanion Technologies 2010a]. This is expressed usually in open positions with Nanion: "Enthusiasm towards excellence in customer support." [Nanion Technologies 2012]

Nanion's customer-facing employees have origins in academia; most of them have a doctoral degree. Therefore, it would be impossible for the firm to operate according to a classical distribution mode. On the other hand, this is also not possible just because the technology is designed so that it can be explained only on par.

There is no-one in the firm who is only active in sales, but all are still involved in the development. That is, they invent things and are involved in new developments ("Technical Service and Development"). Every eight weeks one of Nanion's employees is traveling, for instance, in the US, mostly two weeks a classical sales trip, perhaps a fair and two or three customer visits. There is generally equilibrium between activities that fits the people [DZP07]. This is reflected in Nanion's 2011 organization (Table 2).

It is important that everyone identifies with the company. And the reason is that their own ideas are implemented, that new products, new applications arise simply because one has tried rhem out. This means the firm is not only innovative during foundation and its early phase, but permanently [DZP07].

Customer-orientation as internalization of the firm's culture resulted from the learning effect during the startup's very early phase. "A second financing round planned for 2003 was not able to be performed because of the poor investment environment, which resulted in a very low capitalization during this phase, but this was not able to curtail the great enthusiasm of the entire team. The focus from a very early stage was on a market launch for port-a-patch which proceeded successfully in the pharmaceutical industry, in life science companies, as well as in academic circles." [Deutscher Zukunftspreis 2007]

Typical requirements for Nanion's employees are, for instance [Nanion Technologies 2012]:

The applicant should have excellent ability to *work independently with strong communication, interpersonal and organizational skills*. The successful applicant must have the ability to work in a *multi-disciplinary, multi-cultural and team-oriented environment* – no fear of technical trouble-shooting and solving technical problems. And marketing and sales means activities including *product demonstrations, installation trainings and trade show participation*.

The basic approach of the firm is: "Do it, try it, fix it." [Fertig 2012].

For Nanion what is *really important is success in the market and satisfied customers*. Therefore, it *works very closely with customers* and targets to provide the best possible support. This gets around, and nothing is more effective than word-of-mouth. Overall, it also benefits greatly from the fact that *its technology actually delivers real added value* [Interview Blog 2007].

What researchers (scientists and engineers) of Nanion actually do is a *customer-facing* process [Runge:p. 711, Figure I.131] – interacting or communicating directly with customers (face-to-face), not a business service feature experienced or seen by a customer. This means chances for new business ideas spread out of the interactions with customers – discussions and seeing and learning how the customer works.

Nanion was able (at least for the first ten years of its existence) to *retain the firm culture* of the foundation and early phase:

"When forming a company, both technology and funding are a must, but ultimately it depends on the people who implement it. It was the feeling with us when we were first to third: Hey, we really move much, we all pull together, which is really fun." "Luckily until now, we could keep that." ("Bei einer Firmengründung müssen sowohl Technologie als auch Finanzierung stehen, aber letztlich hängt es an den Leuten, die es umsetzen. Das war bei uns, als wir anfangs zu dritt waren, das Gefühl: Hey, wir bewegen richtig viel, wir ziehen alle an einem Strang, das macht richtig Spaß! Das haben wir uns glücklicherweise bisher erhalten können.") [DZP07]

Innovation Persistence, Expansion and Diversification

After 2006 Nanion was growing organizationally and constantly. The proportion of academic customers (from universities and public research organizations) was roughly two thirds versus one third from industry (pharma and biotech). But by 2009 this changed to an approximately 1:1 proportion [Deutscher Zukunftspreis 2009]. Industrial customers are split into those using the products in house and those purchasing and using them for outsourced testing as fee-for-service providers.

Around 2006 Nanion distributed two generations of patch clamp devices globally. The significant markets were the US and Japan, where Nanion established sales offices and branches [Adam 2009] (Nanion Technologies, Inc. founded in 2009 [Nanion Technologies 2009b]). And Niels Fertig regarded Nanion well positioned for the coming years. His maxims are "*innovation persistence*" [Runge:ch. 4.2.3, Figure I.117, Figure I.127] and *organic growth* [Runge:ch. 4.3.2, Figure I.127].

Customers were captured from all over the world. By 2009 particularly many new customers were from India due to India's pharma market and its pharma's strong position for various forms of cooperation with Western pharma firms. In Russia Nanion began promoting its products [Deutscher Zukunftspreis 2009].

In 2011, to meet the needs of the rapidly expanding number of customers in China, Nanion's dedicated sales- and support team in Beijing opened another branch, Nanion Technologies China.

These branches cover six Nanion employees: Sales&Support Japan (1), Sales&Support USA (2), Sales&Support China (3) [Fertig 2012].

> The best strategy for the future is to continuously create new innovations ("*innovation persistence*") and to *develop high-quality products* ("Die beste Zukunftsstrategie ist es, ständig neue Innovationen zu schaffen und daraus hochwertige Produkte zu entwickeln") [Deutscher Zukunftspreis 2009].

In 2009 Nanion had no bottlenecks concerning financing and no need for a credit. *It could develop on its earned cash flow!* "But in case then the Savings Bank Munich Starnberg will be a reliable partner" for Nanion [Kreissparkasse München Starnberg 2009] and, together with Andrea Brüggemann as managing director and as scientist by education, he continued

> "Today, I am convinced that you can get on with a competent financial service provider like the Savings Bank Munich Starnberg and a good tax consultant without an education in business administration."
> (in German "Heute"bin ich der Überzeugung, dass man mit einem kompetenten Finanzdienstleister wie der Kreissparkasse München Starnberg und einem guten Steuerberater durchaus ohne betriebswirtschaftliche Ausbildung zurecht kommen kann."

In 2009 also a consolidation of the owners/partners of the GmbH (LLC) took place.

After launch of Port-a-Patch (2004; 50 data points per day) and Patchliner (2006; 500 dp per day) in 2008 Nanion announced SyncroPatch 96 (5,000 data points per day) and launched it in 2011 as a response to market demand [Nanion Technologies 2008; Fertig 2012].

The complexity of the scale-up from Patchliner to SyncroPatch 96 and associated long duration of development (ca. three years) was a new challenge to Nanion. It had to learn professional project management [Fertig 2012].

The *opportunity* for Nanion resulted from a discrepancy between the requirement of industrial drug screening of ion channels and the potential of high quality patch clamp automatons which are commercially available. The pharma industry needs higher throughput and lower cost per data point with guaranteed quality of the data. The SyncroPatch 96 exactly met these requirements by providing high throughput, high quality patch clamp recordings, at a low enough cost compatible with industrial ion channel screening requirements.

The SyncroPatch 96 acquires simultaneous recordings from 96 individual cells in a well-plate format. *The SyncroPatch 96 provided the highest throughput in the market for high-quality ion channel screening* [Nanion Technologies 2008]. Hence, SyncroPatch 96 allows testing simultaneously 96 drug candidates. In this way one can record 5,000 data sets per day – ten times as much what can be done with the previous top product of Nanion, the 8 channels Patchliner which is wide-spread with academic customers [Deutscher Zukunftspreis 2009].

By 2011 Nanion's SyncroPatch 96 had convinced big pharma automated patch clamp users and the conclusion of Niels Fertig was: "We see a general trend that experienced APC users decide for the SyncroPatch 96. For us, this is a clear indication that the platform delivers what industrial screeners want, in terms of throughput, experimental capabilities and data reliability. Secondly, experienced users challenge the platforms harder – which we welcome, since it proves the capabilities as well as limitations of the tested platforms. As always, we listen carefully to what our customers tell us, to match their hardware and software requirements." [Nanion Technologies 2011].

Diversification of Nanion did not proceed only vertically, but also horizontally. They developed *new applications of their technology*. In addition to use real body cells pharmacologists and biologists can now also use its equipment for *artificial cells, known as lipid vesicles*.

The advantage of this development is: also ion channels which are not open to traditional methods can be utilized for developing drugs. Moreover, the measurements become simpler as the researchers need not take into account the variety of physiological features when using real cells [Deutscher Zukunftspreis 2009].

Nanion's Vesicle Prep Pro® is the *first product on the market* for automated preparation of solvent-free giant unilamellar vesicles (GUVs). The GUVs are formed by means of electro-swelling. This method yields GUVs of homogenous size (1 - 30 µm in diameter). GUVs prepared with the Vesicle Prep Pro® have proven ideal for investigations of biophysical properties of, for instance, electrogenic transmembrane proteins, lipid raft formation, and protein-DNA interactions.

All of Nanion's patch clamp platforms use Nanion's proprietary NPC® -chips as their primary *consumables* (Port-a-Patch®: NPC®-1; Patchliner®: NPC®-16; SyncroPatch® 96: NPC®-96). These are single-use disposables and are optimized for low liquid consumption and fast perfusion. The NPC®-chips differ from one another in the number of recording sites that are available per chip and the structures in place for liquid handling. Instruments and related consumables are by the same provider.

Nanion also offers a dedicated bilayer (BLM) setup as a turnkey solution that uses microstructured glass chips for patch clamp recordings from lipid membranes. It is a complete system that compromises everything needed for bilayer recording [Innovaro].

The success of Nanion Technologies GmbH is also reflected in 2011 by a new Munich address. Nanion had grown out of its old facilities and can occupy double the size of the old Munich office! With its 1,500 m2 Nanion will have plenty of space for:

- Expansion of the technical development
- Expanded and increased production lines
- Running labs for courses, assay development and product demonstrations.

In 2012 Nanion celebrated its 10th anniversary and as a strongly innovation-driven company we hear from Michael George, CTO and co-owner of Nanion Technologies [BioM 2012]:

"2012 will be a thrilling year, with several different new products in the pipeline. At Nanion, innovation never ends. This is true as much for brand new ideas and concepts as for existing products. Our customers continue to inspire us to develop hardware and software allowing novel experimental possibilities or just making life easier for the every-day-user. It is very rewarding to get the feedback that we are developing state-of-the-art products enabling completely new strategies for ion channel screening and research."

Note added in proof: Customers' numbers by the end of 2013: 65 Pharma/Biotech Companies and 140 Research Institutes

Organization

As described in "Corporate Culture" Nanion's corporate culture means essentially science, people, team, networking and personal contacts with customers. It has a very flat hierarchy; everyone must take responsibility. This means, structures must emerge only when needed.

Nanion's fundamental *activities* determining the firm's structure include

- Customer-orientation
- R&D
- Innovation and investment persistence: continuously new products and product improvement and
- Cash flow based organic growth.

With ca. 60 percent of its workforce being scientific/research employees (most of them with a doctoral degree) it is impossible for the firm to operate according to a particular distribution mode. No-one in the firm is active in only sales, but all are still involved in the development.

Furthermore, it uses *a strategic network of experience and knowledge* (external resource management!) as a strong basis for developing exceptional products.

Challenges of growth (Table 3) cover the following aspects

- Growth of personnel may proceed via "growth thresholds" which require change of organization [Runge:ch. 4.3.1, Table I.72]
- Requirements on the activities of the founders change (desire/willingness to change)
- Clear, well-defined and structured business processes become increasingly important.

Growth of Nanion additionally showed further challenges [Fertig 2012]

- Technical Development vs. Marketing & Sales (D vs. USA)
- With increasing installed customer base the need for technical service in terms of finances and manpower must not be underestimated.

Nanion's leadership team (Management & Board) evolved over time:

- Niels Fertig, CEO, PhD (Co-Founder, 2002)
- Michael George, CTO (2002; First Employee)
- Andrea Brüggemann, CSO, PhD (joined 2003)
- Cecilia Farre, Marketing Director, Senior Scientist, MSc, PhD (joined 2006)
- Rodolfo Haedo, General Manager and Chief Scientist, Nanion, Inc. (US)
- Professor Jan Behrends (Co-Founder, 2002), Chairman of the Board.

Though Nanion's organization is only described for 2011/2012 (Table 2) its development proceeded in a common way. The development is reflect by the "10 – 25 – 150" rule of thumb [Runge:Table I.72] relating the number of employees to requirements of re-organization – relating the number of employees to organizational issues, such as leadership/management, specialization, communication, coordination and delegation.

In particular, in the context of the launch of the Patchliner Niels Fertig explained: "Sticking points for *organizational problems* occur with *ten to fifteen employees*. Then, *internal communications* becomes the decisive factor for the future development." (in German "Knackpunkte für Organi-

zationsprobleme treten bei zehn bis fünfzehn Mitarbeitern auf. Dann wird die interne Kommunikation zum entscheidenden Faktor für die weitere Entwicklung.") [Fertig 2012]

Concerning the "25 threshold", when having won the German Founders' Award ("Deutscher Gründerpreis") in 2009 with 29 employees (Table 3), Niels Fertig concluded "We have achieved a size which requires new structures."("Wir haben jetzt eine Größe erreicht, bei der man neue Strukturen braucht") [Deutscher-Gründerpreis 2009; Adam 2009]

Table 2: Team Nanion 2011/2012 [Fertig 2012].

Units	**Remarks**
Management Team (3)	The "core" (Fertig, Brüggemann, George)
Technical Development and Support Team (10)	"R&D"
Applications and Customer Support Team (10)	"TS&D" (Technical Service & Development")
Production and Internal Support Team (12)	"Production"
Marketing (1)	Minimum "classical" marketing
Sales&Support Japan (1)	Nanion has currently a worldwide distributor network, in North America, Europe, China, Russia, Japan, Korea, Taiwan, Singapore, India
Sales&Support USA (2)	
Sales&Support China (3)	

Promotion and usage of Nanion's products and news were supported by establishing "Nanion Notes" on its Web site; the first issue (of May 2005) introduced the Port-a-Patch, the fourth issue introduced the Patchliner [Nanion Technologies 2007b].

Later Nanion also offered Webinars for its customers and potential customers and hold Patchliner and SyncroPatch User Meetings.

Now with a worldwide network of distributors Nanion is always in the time zone of the customers! Nanion's service activities range from training to service contracts and on-site visits to make the road smooth for customers, so that everyday routines run optimally, and the user gets the most out of its products and their time (product delivery in person, information and demonstration on site).

Nanion offers training in electrophysiology, including assay development and data analysis. All training is adapted to the participants' experience to maximize the benefit.

A Service Contract is usually a service and support package covering any part of the purchased platform. The Service Contract includes hardware maintenance, software updates and technical support via email and telephone. Additionally the customers also have access to Nanion's expertise in electrophysiology. Scientists are available to help with electrophysiological questions, assay development and data analysis. A yearly service check may also be included, involving maintenance or replacement of robotic parts.

Furthermore, with the service contract Nanion also offers hardware and software customization and adaptation of data input and output to ensure straightforward integration with existing database systems.

Vision/Mission, Business Model

Nanion combines bio- and microtechnology in a company serving academic and publicly financed research in life sciences and serving the life sciences industry by offering products and services which will dramatically increase the speed and efficiency of the drug discovery process in an important segment of the pharmaceutical market.

Nanion bases its business on a proprietary chip technology and will design and develop high throughput screening (HTS) systems for ion channel active drugs (ICADs). Ion channels are prime targets for innovative medicines aimed at many important diseases.

The *vision* "inspired by scientists" is the definitive essence which provides the basis of all Nanion activities and products. Scientists work together with engineers and designers. – teamwork across disciplines and functions.

Its *mission* (on its Web) means: Nanion Technologies – Smart Tools for Ion Channel Research, Drug Discovery, Automated Patch Clamp.

And Niels Fertig regarded Nanion well positioned for the coming years based on a solid business model. His maxims are "*innovation persistence*", *high-quality products* and *organic growth*:

- The best strategy for the future is to continuously create new innovations ("*innovation persistence*") and to *develop high-quality products* („Die beste Zukunftsstrategie ist es, ständig neue Innovationen zu schaffen und daraus hochwertige Produkte zu entwickeln." [Deutscher Zukunftspreis 2009]
- "We … look forward to a future where we are committed to continued organic economic growth." [Nanion Technologies 2010a]

According to Niels Fertig "We work in a high technology field and have a clear *premium* strategy. We believe that we provide a great value and skim it off also with the customer." "We provide a very large part of the company's value chain; we buy some parts; we cover a lot of suppliers, as mechanical work or circuit boards. They can be reached in Munich by bike." [DZP07]

And related to the quality aspect and the issue of outsourcing Andrea Brüggemann added: "We are in a very sensitive area in terms of quality. And for that reason I think that it is very difficult for us to outsource." [DZP07]

Inspired by science and building on experience to create the future mean the following.

Innovation results from a combination of intensive research, applied methodology, an unprecedented power of observation and, not least, a great passion. "We live science and are constantly pushing the boundaries."

Innovation at Nanion follows this pattern. Knowledge from scientists from different disciplines is brought together to form a solid background on which to expand ("interdisciplinarity"). Nanion knows from experience, particularly personal contacts, what the customers demand and need ("latent needs").

- Solid expertise is in technology, engineering and software development (also customization of hard- and software).
- There is broad electrophysiology experience.

Nanion Technologies was founded in an academic and creative environment and uses a strategic network of experience and knowledge as a strong basis for developing exceptional products ("external resources").

Nanion presents a "Unique Selling Proposition" (USP): "What we do is rather special." ("Was wir machen, ist ziemlich speziell.") [Mayerl 2010] It addresses customers in a variety of ways with clearly seen advantages by the customers.

Basically development of all *products* at Nanion underlies principles of *easy handling* by customers focusing on *familiarity* with the operational mode. In particular, patch clamping is designed as easy as running a Polymerase Chain Reaction (PCR) device which is a common instrument used in the customers' labs.

The integrated design of this technology makes it a *quickly installed* and an easy to use system. The software and data acquisition system is compatible with other standard electrophysiology software data formats [Innovaro].

Accelerating patch clamping by HTS means saving time and cost and for the drug discovery process (Figure 2) getting additionally results with much less uncertainty whether a substance acts or interacts with a given target structure – contrary to, for instance, optical measurements. It avoids early targets which will exhibit side effects and will not comply with regulatory requirements.

Nanion's products are appreciated because of their vast experimental freedom paired with increased throughput and affordable consumables.

Concerning consumables, it would be interesting to know, whether and in how far concerning revenue streams Nanion follows a *razor-blades business model*. Just like Gillette makes money by selling consumable blades or, before digital cameras Kodak made profits on the continuous consumption of film, rather than on selling cameras, this model for generating revenues is attractive.

Nanion will keep *competitive advantage* essentially based on protected technology, intangible assets and resources, intellectual capital (IC) and organizational capital [Runge:p. 54,55; TableI.8]. This includes essentially leadership, employees' competencies and identification with the firm and corporate culture as well as customer relationships and broad experience and a network as an external resource.

Critical success factors (CSFs) are:

- "The *team is the main asset* that we currently have. With the people we can move very much, and all have fun." ("Das Team ist das Haupt-Asset, das wir aktuell haben. Wir können mit den Leuten sehr viel bewegen, und alle haben Spaß daran.") [DZP07]
- Have its technology sufficiently protected. Withstand potential threats of patent suits potentially initiated by any "deep pocketed" competitor concerning the basic Nanion technology.
- For growth hire competent people who fit Nanion's corporate culture.
- Keep *customer-oriented and customer-facing attitudes and processes*.
- Capture customers from all over the world.
  By 2009 particularly many new customers were from India due to India's pharma market and its pharma's strong position for various forms of cooperation with Western pharma firms. Nanion began promoting its products in Russia also in 2009 [Deutscher Zukunftspreis 2009].
- Customers continue to purchase Nanion's products and prefer to run in house the majority of their ion channel testing activities rather than outsource them.
- Generate enough cash flow to finance further growth and keep independency of Nanion.

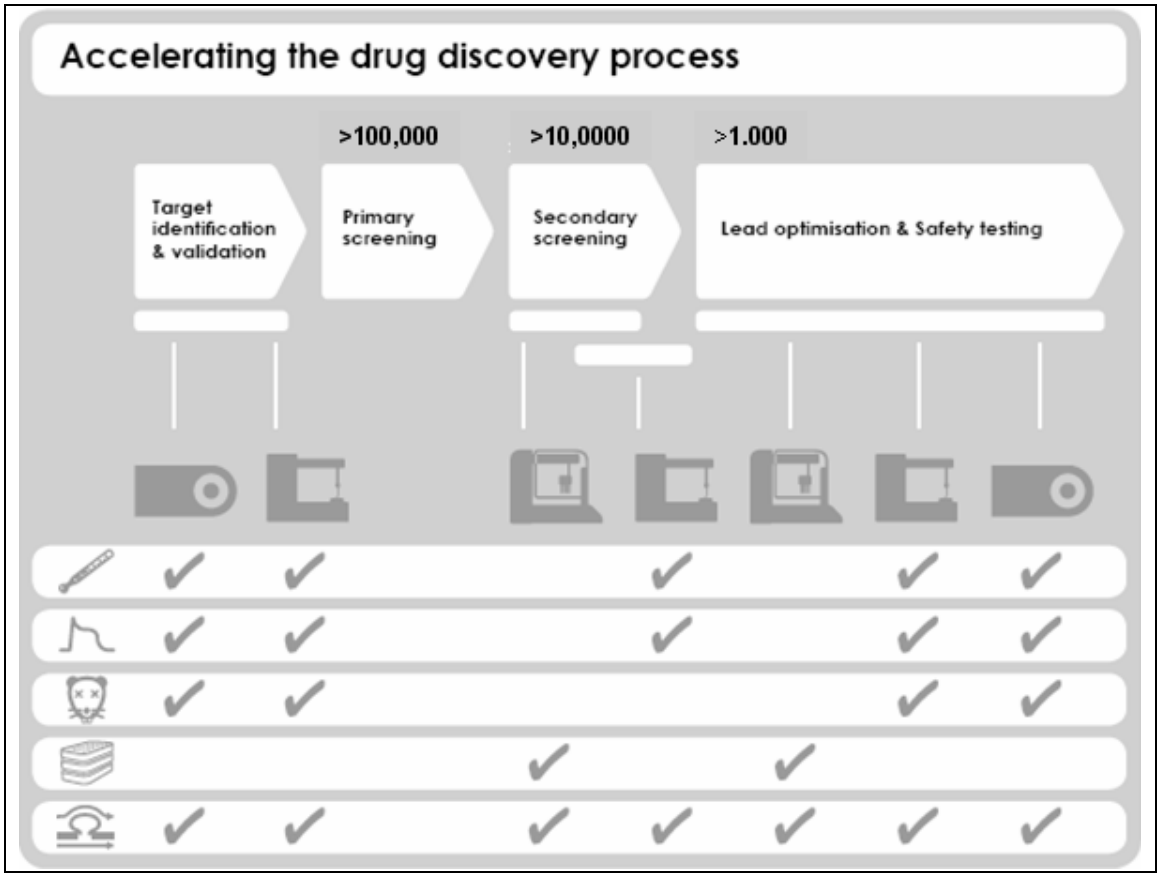

Figure 2: The drug development process and the roles Nanion Technologies' products play [Nanion Technologies 2010a].

Key Metrics

Nanion shows a significant growth story, if revenue or number of employees is used as growth indicators.

Nanion's revenue primarily comprises

- Sales of its patch-clamp devices,
- Sales of related consumables for the devices
- Consulting services,
- Fees from research and development projects that are conducted on a contractual basis for third parties (called customer-sponsored research and development projects).

In 2004, two years after firm foundation, Nanion recorded already a profit and since then was always profitable. This early success is exceptional for top-value technology (TVT) NTBFs [Runge:Table I.1].

According to Mayerl [2010] of the 30 employees (in 2010) two thirds are academics, most of them with a doctoral degree.

The individual contributions of the various sources of revenue are not known and also not the contributions of the various types of patch clamp or other devices. Concerning consumables their proportion to the overall revenue streams is also unknown, but may be significant.

Nanion's revenues and number of employees as extracted from various sources are given in Table 3. As Nanion usually runs publicly financed projects the actual manpower includes full-time employees and also part-timers. For instance, by 2007 Nanion had 16 full-timers and ca. 10 people as part timers. This would mean an overall workforce of ca. 20 full-time equivalents [DZP07]. It is not known whether public project money is included in the available revenue data.

Though Nanion has a strong international orientation there are no data on its export rate. On the other hand, the branches and distribution centers abroad (Table 2) suggest a rough estimate of the export rate to be 30 percent. Furthermore, it is not known in how far Nanion's revenue is sensitive to currency exchange rates.

The tremendous jump in revenues from 2006 to 2007 showing a growth rate of roughly 100 percent and then further growth of ca. 30 percent should be essentially due to the launch of the Patchliner in 2006 – "bracket" [Runge:ch. 4.3.5] for its further development.

Table 3: Development of Nanion Technologies in terms of number of employees and revenues *).

Year	Number of Employees	Revenues (€, mio.)
2002	Foundation - 2	
2003	3 (minimum)	
2004		Profitable!
2005	7 ([ENNaB 2004]; by Sep. 2004)	0.507 1)
2006	{11} 12 [Bavarian Government 2006]	1.3 2)
2007	{15} 20	2.6 [Deutscher Zukunftspreis 2009]
2008	{22}	3.2 [Adam 2009; Deutscher Zukunfts-preis 2009]
2009	{28} plus 1 in USA;	4 [Kreissparkasse München Starnberg 2009]
2010	30 [Mayerl 2010],	
2011	>40 [Fertig 2012]; 42 [Bayern International 2013] 3)	> 7 [Fertig 2012]

2012		
2013	> 50 [Aif 2013]	

*) All the data are from the given references, data in braces are from the German official legal document “Elektronischer Bundesanzeiger” (Electronic Federal Annoumcements), others are from the given references.
1) Niels Fertig personal communication; 2) €1.3 mio.estimated in line with estimates of €1.2 mio. for NTBFs in the fifth to seventh year of existence and having 9 employees [Runge:TableI.71];
3) employees in Bavaria.

The focus on the health area and pharmaceutical industry as well as (largely publicly funded) research in universities and research institutes makes Nanion’s business rather insensitive to economic recessions. Its growth (revenues, employees) continued across the Great Recession without a major perturbation. It is on a path to become a “Hidden Champion” [Runge:ch. 4.1.1].

Intellectual Properties

Product and biochip tradenames are branded.

Concerning Nanion’s patent situation according to Niels Fertig “We are secure, we made our own applications very early; in the meantime we bought also patents and are in a very well position.” [DZP07]

Nanion has about eight patent families with the basis patent documenting the three founders as inventors being:

Titel: Biochip, used in probe for investigating ion channels, has substrate with opening(s) to receive cell membrane with ion channel(s).

Inventor	**Applicant**	**Publication info**	**Priority date**
Fertig Niels; Tilke Armin; Behrends Jan; Blick Robert	Fertig Niels [DE]; Tilke Armin [DE]; Behrends Jan [DE]; Blick Robert [DE]	DE19936302 (A1) 2001-02-15	1999-08-02

Nanion was engaged in a patent suit with the firm Molecular Devices Corp. (MDC) and in 2007 announced that they would appeal the decision of. the European Patent Office (EPO) to uphold the disputed Molecular Devices patent EP 1,040,349 [Nanion Technologies 2007a].

The appeal was merely *a precaution against problems with future developments in the field*; the disputed patent had no relevance for Nanion’s marketed products, such as the Port-a-Patch or the Patchliner. Andrea Brüggemann, CSO at Nanion, commented: "Our customers should know that this patent dispute in no way concerns our present planar patch technology, nor indeed those marketed by Molecular Devices.” Rather, the disputed patent sought protection for a well-known physical effect that theoretically can be used to exert electrical force on cells or vesicles.

"All currently marketed planar patch-clamp devices use suction to move cells, not electrical force, which so far has proved unreliable. However, all of them, and many other devices published long before MDC’s patent can produce such electrical forces if enough voltage is applied," explained Nanion's CEO Niels Fertig.

The disputed patent was originally filed by the Ecole Polytechnique Fédérale in Lausanne, Switzerland and then taken over by Cytion SA, a start-up company acquired by Molecular Devices in 2001 and shut down shortly after.

In its originally granted version, the patent claimed protection for all devices that can be used to move cells towards an aperture with electrical force. While all currently marketed automated patch clamp (APC) devices use suction rather than electrical force to position cells or vesicles, these devices – as well as *devices published long before MDCs patent was filed* – are, in principle, able to produce such electrical forces.

In 2010 Niels Fertig, Nanion's founder and CEO stated: "After nearly eight years of opposition against this patent, we are pleased that the final instance of the EPO has removed *a potential threat to further development in the field*." (Emphases added) And Andrea Brüggemann added: “This decision now finally removes even the remotest possibility of IP issues with current and future Nanion products with respect to the opposed patent." A Board of Appeal of the European Patent Office (EPO) had overturned an earlier decision of the Opposition Division to uphold patent EP 1,040,349 owned by Molecular Devices, Inc. (MDC) [Nanion Technologies 2010b].

Jan Behrends, Nanion's co-founder and chairman of the board concurred: "In effect, this final decision secures freedom to operate for everyone marketing or developing automated patch clamp devices with respect to the opposed patent. Besides, it contributes to a fair appraisal of important work done long before the patent."

Competition

The number of Nanion’s competitors is very small. Niels Fertig explained “There are only a handful of providers for these analysis devices worldwide.” [AiF 2013]. One of them is Molecular Devices. And the self-confident Niels Fertig stated: “We will continue to grow. We drive the field in front of us.” (“Wir werden weiter wachsen Wir treiben das Feld vor uns her.”) [Mayerl 2010]

In the early days competition was with other small firms in Germany, Cytocentrics AG and Flyion GmbH, Sophion Bioscience A/S from Denmark, Axon Instruments from the US and Molecular Devices Corp. (now an LLC and part of a large US firm) (Table 4). Both, Sopheon and Axon, were later acquired by large instrument firms.

It is interesting to note that there exist patents having simultaneously Nanion and Cytocentrics as the assignees. This is part of a large global patent family: Verfahren und Vorrichtung zum Messen an in einer flüssigen Umgebung befindlichen Zellen (Method and device for taking measurements of cells which are contained in a liquid environment) with a priority date of 1999-10-08 (DE1999148473 19991008) and inventors/assignees from Tübingen/Reutlingen and NMI (→ Cytocentrics) and Bayer AG. Nanion occurs as an assignee only for a restricted number of countries.

Table 4: Early competitors of Nanion Technologies and their products [Comlay 2003; Hogg et al. 2006].

Company	**Products**
Cytocentrics AG (Rostock, Germany; till 2004 Cytocentrics CCS GmbH, Reutlingen, Germany)	CytoPatch™ Automat
flyion GmbH (Tübingen, Germany)	Flyscreen® 8500
Sophion Bioscience A/S (Ballerup, Denmark)	QPatch 16
Axon Instruments, Inc. (US) (Union City, CA, US; acquired 2004 by MDC)	PatchExpress® 7000A. OpusExpress® 6000A
Molecular Devices Corp. (MDC) (Sunnyvale CA, US)	Ion Works® HT, IonWorks® Quattro™; OpusExpress® 6000A; PatchExpress® 7000A

When Nanion offered recently positions on its Web site for Application Scientists requirements do not only referred to strong customer orientation: “Enthusiasm towards excellence in customer support.” Nanion is well aware of counter-products (directly competitive products) in the market. It is appreciated, if the applicant has experience with counter-products: “Experience of automated patch clamp platforms (Patchliner, IonWorks, QPatch, or PatchXpress) is considered very posi-

tively for the applicant." This indicated that Nanion regards currently essentially two large companies as its rivals – Sophion Bioscience and Molecular Devices with which it had a patent suit.

Sophion Bioscience, headquartered near Copenhagen, Denmark focuses on providing state of the art products and integrated solutions for automated patch clamping. Sophion Bioscience was founded in July 2000 as a spin-off emerging from a successful research and development program at the biopharmaceutical company NeuroSearch A/S with headquarters in Ballerup, Denmark and facilities in Gothenburg, Sweden. The headquarters are located in the vicinity of Copenhagen, Denmark. For international support and sales Sophion has a US office and a branch office in Japan (since 2009). It planned expansion to include staff in China [Ballerup 2011].

In 2011 Ratos's subsidiary Biolin Scientific AB (an instrument provider from Sweden) signed an agreement to acquire all the shares of the Danish company Sophion Bioscience A/S. In 2010 Sophion's sales totaled DKK 83m (ca. €11.2 mio.) with an operating profit (EBITA) of DKK 8m [Ratos 2011]. In 2011 Sopheon had 42 employees [Ballerup 2011] comparable with the number of employees of Nanion (Table 3).

According to the Danish financial newspaper Børsen Sopheon became a Gazelle company [Runge:p. 557,562]: In 2010 it has had a continuous growth in both turnover and gross profit during the past four fiscal years and which, all together has doubled its turnover or gross profit in that period (from Sopheon's Web site).

Notably, Sophion currently offers Rent-a-Resource service to use if complex challenges occur in relation to its QPatch (QPatch 16 and QPatch HT – 48-channels) or Qube experiments. A Sophion application scientist will come to the customer's lab to work with him/her. Sophion's new next generation high-throughput system for ion channel screening product Qube is intended for use in laboratories with a need for thousands of data points per day.

The QPatch product family comes in three versions, with 8, 16 or 48 simultaneous and individually controlled patch clamp recordings for QPatch 8, QPatch 16 and QPatch HT. The Qube provides 384 simultaneous recordings. All consumables necessary for the daily operation of QPatch are available from Sophion.

By the end of 2013 Nanion launched the SyncroPatch 384PE automated patch clamp system. The SyncroPatch 384PE (Patch Engine) is the industry's highest throughput giga-seal system scalable to 768 channels, and is capable of 20,000 data points per day.

Both the German startups, flyion and Cytocentrics, had roots in the University of Tübingen and were founded in the same year. flyion GmbH was founded in 2001 as a spin-out of the Institute of Physiology at the University of Tübingen (Germany). Cytocentrics was also founded in 2001. This means, around 2000 there was something *"in the air*" with regard to automate patch clamping (Sophion Bioscience founded in 2000). Hence, foundation of Nanion was associated with *urgency*.

The company was founded by Dr. Albrecht Lepple-Wienhues (physician and biophysicist), Dr. Klaus Ferlinz, (chemist and molecular biologist) and the management consulting company i.con innovation GmbH. As a third partner for the management team Dr. Philip Witte (businessman) joined flyion in the fall of 2002. Investors were the SEED group (lead investor with 24.6 percent) and the Berlin Special Funds for Biomedical and Medical Technology Mediport venture (21.6 percent). Tbg (Technologie-Beteiligungs-Gesellschaft mbH) owned by the Federal Government acted as compensation silent partner [flyon 2003].

Flyion's Flyscreen®8500 was an automated patch clamp robot utilizing standard glass capillaries, a 3 or 6 channel version of the robot.

flyion developed the Flip-the-Tip technology, providing full automation of the standard patch clamp technology so that several cells can be recorded simultaneously:
A standard borosilicate patch pipette is glued into a plastic jacket forming the entity of the FlipTip®. The FlipTip® is positioned tightly into a recording socket which has been filled with intracellular solution. Extracellular solution is then back-filled and rather than finding a cell with the FlipTip®, a cell suspension of only a few thousand cells is automatically dispensed from a cell hotel into the back of the FlipTip® [Fejtl 2005].

By 2010 the L-Bank, a public bank owned by the government of the federal state Baden-Württemberg, held equity interest of 41.18 percent, increased from €322,000, or 32.15 percent in 2009 [L-Bank 2010]. But, finally, according to BioNode [2012], flyion GmbH became insolvent in August 2012.

Cytocentrics CCS GmbH was co-founded by Dr. Thomas Knott. But he was one of the driving forces behind the foundation of Cytocentrics since 2001. He took over leadership in development.

Prior to founding Cytocentrics, Dr. Knott had a postdoctoral research position at the NMI (Natural and Medical Sciences Institute at the University of Tübingen, Germany), where he completed a "Proof of Principle" of an automated patch clamping technique by which he provided the basis for the foundation of Cytocentrics. Dr. Knott graduated in biology at the University of Tübingen and holds a doctorate in neurobiology from the same University with an emphasis on electrophysiology and microelectrode array application.

Thomas Knott designed the concept of automatic patch clamping already in his dissertation at the University of Tübingen [Anonymus 2007]. As a "postdoc" he wrote a business plan, and in 2001 founded the company Cytocentrics in Reutlingen in the South-West part of Germany close to Tübingen. He achieved to get the patch clamp Nobel Prize winner Erwin Neher as a scientific adviser.

The company's product portfolio did not only include devices such as the CytoPatch™ Automat and consumables such as the CytoPatch™ Chips. Cytocentrics also offered made-to-measure screening services for which the client only needs to supply the substances that are to be examined [BioPro 2004).

The survival of the Cytocentrics after foundation was "guaranteed" essentially by public funds and projects [BioPro 2004), but it needed much more money to prepare its product for the market. Via the German Association of Private Equity and Venture Capital Companies (Bundesverband Deutscher Kapitalbeteiligungsgesellschaften) the founder was directed to Genius Venture Capital GmbH (Schwerin, federal state of Mecklenburg-Vorpommern) focusing on early-stage-financing.

Cytocentrics became a private stock company in 2004, but had to move to Rostock in the very North-East of Germany in 2006. Cytocentrics hoped in 2008 to produce the prototype of its patch-clamp machines produced in Mecklenburg-Vorpommern. Three pre-production units of the patch-clamp machines were running in Rostock [Anonymus 2007].

The contribution of Genius Venture Capital to Cytocentrics is not known. However, it reported other investments [Genius VC]:
In 2008 the Düsseldorf-based venture capital firm investor Stars Innovation AG provided growth of two million euros for the entry into international markets. The new funding should allow Cytocentrics to be better positioned as a screening service for the pharmaceutical industry. According to Cytocentric experts estimated the total market volume for Cytocentrics offerings to be $350 million.

In 2011 Cytocentrics completed another financing round of €1.1 million. The investors were from Buschier Group of the South Tyrol (Italy) focusing on growth companies and the state-owned German KfW Banking Group (ERP Start Fund). These funds should expand administration and manufacturing equipment and intensify international sales.

Cytocentrics lacked focus. Apart from ion channel measuring devices Cytocentrics with a subsidiary in the Netherlands was active in a number of technologies, such as microchip development and production, microfluidics, cell biology and the development of amplifier technologies for the mega-ohm range.

By October 2011 Cytocentrics AG started the preliminary insolvency proceedings ("vorläufiges Insolvenzverfahren") [HGW 2011]. As a result a new firm was founded (Cytocentrics Bioscience GmbH). Partner of Cytocentrics Bioscience GmbH is primarily the Buschier AG (84.82 percent), a shareholder of Cytocentrics AG who it once again pleaded for the company and secured future funding [HGW 2011].

By the transfer of the business 14 jobs at the headquarter and three jobs in the Netherlands could be secured, without pre-existing liabilities. Furthermore, the results of the established technologies were preserved and thus a potential for an envisioned future development could be protected [HGW 2011].

According to HGW [2011] the background for bankruptcy was a failed round of financing in which the existing investors could not agree on common terms. But people knowledgeable with the matter put forward business reasons: It took too long to launch the first product into the market and the product was too complex.

Hence, Nanion currently competes essentially against two large firms (Sopheon and Molecular Devices), as also the new Cytocentrics does not represent a threat.

Molecular Devices Corp. (MDC), founded in 1983, grew by a number of acquisitions. Particularly MDC Molecular Devices acquired the patch clamp firm *Axon Instruments* (PatchXpress 7500A) in 2004. In March 2007, Molecular Devices was acquired by MDS, Inc. (Toronto, Canada) and became part of MDS Analytical Technologies. In February 2010, Danaher Corporation acquired MDS Analytical Technologies, and Molecular Devices, Inc. now operates within the Danaher Medical Technologies segment as an LLC. Danaher is a large global US company (in 2012 $3.165 billion and 63,000 employees) [Wikipedia-2]. Molecular Devices LLC was founded in 2010.

Axon Instruments, Inc. (founded 1983) produced a broad spectrum of instrumentation and software for cellular neurosciences, genomics, and cell-based screening focusing on drug discovery aimed at the pharmaceutical industry, biotechnology companies, and academic researchers. Axon's PatchXpress 7000A was a great success in the US. It shipped 20 units in only five months, and, having a significant number of orders in the pipeline, generated satisfaction that the firm had succeeded in its product goals. It claimed PatchXpress 7000A to be the world's first commercially available automated planar patch-clamp workstation for true, tight-seal whole-cell voltage clamp [PRBewswire].

Molecular Devices produced its first microplate reader in 1987. Since then, the company has continued to advance scientific instrumentation and software for a wide range of bioanalyses. It supplies various analytical systems, including instruments, software, and reagents, to accelerate and improve drug discovery and basic life science research in industry and academic research. Patch clamp systems is just one particular offering.

It claims to provide one of the widest ranges of bioanalytical measurement systems, software and consumables for life science, pharmaceutical and biotherapeutic development and drug discovery research available from a single supplier. Molecular Devices has essentially two product families based primarily on the customers to which they are sold, the drug discovery product family includeing the APCs and the life sciences product family, which includes bench-top detection, imaging software and liquid handling products.

Current patch clamp products include PatchXpress 7000A and IonWorks Quattro Systems. The IonWorks Barracuda Plus system launched in 2013 allows for complete dose response curves to be generated in single wells, thereby reducing running costs and increasing throughput. Unlimited compound additions can be made to wells in a 384-well PatchPlate™ generating up to 384 dose response curves.

Before being acquired by MDS Inc., by the end of 2006, Molecular Devices had revenues of $186 mio. and 543 employees. In 2013 it is still at $186 mio. and Research & Development (R&D) as percent of revenue was 12.5. [4]

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Notes

1. The 1991 Nobel Prize in Physiology or Medicine was rewarded to Erwin Neher and Bert Sakmann's for creating the experimental measuring device that conclusively proved the existence and function of ion channels. The patch-clamp technique is based on an exquisitely simple idea. An extremely fine glass pipette with a very small opening is used to make contact with a tiny area, or patch, of the cell's outer membrane that, with some luck, will contain only a single ion channel. Applying a small amount of suction through the pipette forms a seal tight enough such that ions can only flow from the channel into the pipette. By fitting the pipette with a highly sensitive electrode, Neher and Sakmann could record every minute change in current produced as ions flow through the clamped channel into the pipette. With their recording device, they showed how these channels function by opening up and closing in nerve cell membranes to allow certain ions through one at a time.

   The patch clamp technique allowed key features of these channels to be defined with fine precision. Specifically altering the genes that encode ion channels and studying the consequences in cells allowed Neher and Sakmann to pinpoint the parts of the channel that open or close and that select which ions can pass through.

   By Sophie Petit-Zeman, for Nobelprize.org (http://www.nobelprize.org/nobel_prizes/medicine/laureates/1991/speedread.html).

2. Ionera: http://www.ionera.de/index.htm.

3. Gigaseal: In the patch clamp process the micropipette is pressed against a cell membrane and suction is applied to assist in the formation of a high resistance seal between the glass and the cell membrane (a "gigaohm seal" or "gigaseal," since the electrical resistance of that seal is in excess of a gigaohm). The high resistance of this seal makes it possible to electronically isolate the currents measured across the membrane patch with little competing noise, as well as providing some mechanical stability to the recording [Wikipedia-1].

4. http://www.mass-spec-capital.com/organisation/molecular-devices-llc-danaher-group-inc-1983-sunnyvale-2001-31331.html (last access 8/18/2013); http://www.advfn.com/exchanges/NASDAQ/MDCC/financials (last access 8/18/2013).

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