

CASE STUDY: BASECLICK GmbH

In recent years, the field of biomedicine has witnessed revolutionary developments that have set major milestones. These developments, including nucleic acids, DNA decryption and modification and labelling methods, have led to significant advances and have resulted in the successful commercialisation of a large number of products and services.

HOW IT ALL STARTED

Set up in 2008, Baseclick, a company located in Neuried near Munich, has a thriving business offering solutions based on their core technology, the "click reaction". Baseclick produces a wide variety of click chemistry optimised products and services, ranging from labelling kits and catalysts to solvents and reagents. The advantages of the product include the broad range of application possibilities, high yields and quick and easy reaction conditions using readily available and inexpensive reagents. Baseclick holds patents worldwide for these applications, which can be used to:

- detect, control and analyse cell proliferation *in vitro* and *in vivo*
- label DNA and RNA for the preparation of, for example, FISH probes
- label nucleic acids and other biochemical molecules

Backed by sound expertise, ongoing research and a good business strategy, Baseclick is now a well-established enterprise with revenue in the two-digit million range. Its path to success was, however, not always straightforward, as it encountered major difficulties when an unexpected event put the project's viability at stake and forced the researchers to reconsider their chances of achieving their aims.

Starting points

In 2003, a group led by Thomas Carell, Professor of Chemistry at Munich's Ludwig Maximilians University (LMU), and supported by a grant from BASF started to research the use of the "click chemistry" discovered by Professor Sharpless of the Scripps Institute, to modify nucleic acids. Together with his PhD students Gramlich, Gierlich and Burley, he began work on optimising the click chemistry reactions for biomolecules. Soon, the group was able to show that most existing DNA labelling methods could be replaced by click chemistry to provide a new labelling system that was fast, reliable, highly specific and high-yielding.

The group demonstrated that, in theory, every base in a DNA strand could be labelled by a functional group. In 2005, this co-operative venture between the LMU and BASF led to the filing of a patent application entitled "*New labelling strategies for the sensitive detection of analytes*". The group's findings were then published in the specialist journal *Organic Letters* (J. Gierlich, G. A. Burley, P. M. E. Gramlich, D. M. Hammond, T. Carell, "Click Chemistry as

a Reliable Method for the High-Density Postsynthetic Functionalization of Alkyne-Modified DNA”, *Org Lett.* 2006, 8, 3639-3642).

TECHNICAL BACKGROUND

Since the advent of DNA decryption, a great deal of research has focused on improving our understanding of how it works, among others for medical purposes. For example, to identify disease-related mutations of the DNA, certain locations of the DNA strands are marked for further analysis. This marking is usually done with fluorescent labels that are attached at different locations of the DNA strand. The techniques for this labelling have been improved constantly over the last 20 years.

Professor Barry Sharpless, Nobel Prize laureate, discovered the copper mediated azido-alkyne cyclo-addition (CuAAC) reaction in 2001. Sharpless named this chemical reaction type “click chemistry”. It allows the addition of fragments to existing molecules to which fluorescent elements can be added. This reaction was simple, clean and generic.

Professor Thomas Carell, founder of Baseclick, adapted this method to the modification of biomolecules, since neither azide nor terminal alkyne functional groups are generally present in natural systems. Alkyne-modified DNA nucleobases are functionalised by the addition of the corresponding labelled azide (e.g. fluorescent-dye-azides) using the CuAAC reaction. This results in the obtention of labelled DNA, and allows tracing of the DNA modifications. Professor Carell and his team further developed the method for nucleic acid modification by adding ligands specific for copper (copper stabilising agents) in the reaction, as copper ions damage DNA. The ligands bind to free copper and protect the biomolecules from degradation (see Fig. 1).

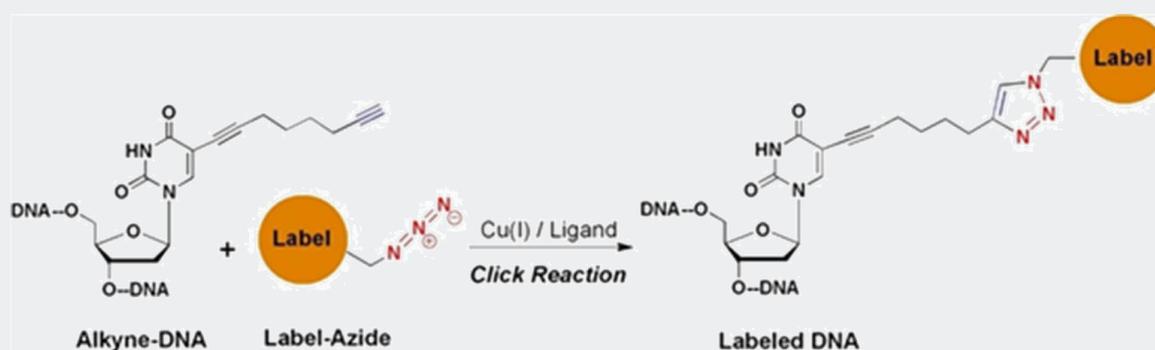


Fig. 1 The click reaction to label nucleic acids

This allows users to label multiple dye molecules on DNA strands in a sequence-specific manner without the by-products produced by conventional methods. The attachment of multiple dyes enables multiple and highly complex analyses to be carried out in a single operation. Applications include analyses for pathogens and tumour cells and the detection of mutations in human, animal and plant genomes.

First steps towards commercialisation

Following the group's scientific breakthrough, Thomas Carell initially envisaged setting up a company to commercialise the invention. The patent held by Professor Carell would protect exploitation of the technology, although they would still need a *licence* ❶ from Scripps, since they were building on Barry Sharpless's invention.

In the meantime, however, BASF had refocused its strategy and had started using the labelling technology for other purposes. As a result, it stopped supporting a number of projects in the DNA field. BASF and LMU tried to find a licensee for the patent. Having failed to do so, by the end of 2007 the idea of establishing a company was once again on the agenda, and in April 2008, Carell and BASF together founded Baseclick. Gramlich and Manetto, both from Carrell's lab, joined the company as its first employees.

BASF and the LMU sold the patent application to Baseclick for a one-off payment and a *royalty* ❷ -based licence fee. In 2009, Frischmuth joined the company as CEO, changing its focus from research to development. The aim was to market the technology competitively. To that end, the production of chemicals using click chemistry to modify nucleic acids was improved to allow them to be made cheaply and on a large scale.

QUESTION

What does selling a patent actually mean?

Having sold the patent, do BASF/LMU still *own* ❸ any rights?

THE CHALLENGE

As Baseclick started to take off, the story took an unexpected and crucial turn with the granting of the patent in 2010: Professor Carell was informed that a group of attorneys representing a powerful US biotech company had filed a patent application (with later priority) and was threatening an *infringement* ❹ lawsuit in the US and an opposition in Europe. For a company still in the start-up phase, this represented an enormous challenge: legal expertise and representation costs before the courts in the US would mean expenditure that it could not afford.

Coming at a time when revenues start to consolidate and investment is still needed, the anticipated costs and the risk of losing the business were a shock. "To be able to defend the patent in the US courts, the first thing I had to do was transfer a six-digit sum to our representatives!" Carell remembers. In addition, there was a further risk that the court might decide to issue an *injunction* ❺ to stop the commercialisation of potentially infringing products.

QUESTIONS

- What were Baseclick's options apart from going to court?
- What does Baseclick need to consider if they decide to go to court?

Litigation proceedings before the courts can be very time-consuming, and their outcome uncertain. As an alternative, the company could have tried to reach a **standstill agreement** ⑥ with the claimant, in order to settle the case out of court. To do that, however, it would have needed to be in a much stronger negotiating position. But it was not in a position to fight in court, nor could it offer anything but access to its technology in the European market, which would have been a very disadvantageous solution.

When it comes to licensing their exclusive rights, patent owners can consider a number of different options: straightforward licences, exclusive licences and sole licences (which exclude the owner from exploiting the invention).

QUESTIONS

- If they win the case, will Baseclick be free to commercialise the invention, or are there any other legal hurdles that may arise?
- What options are available to them if they go to court and lose the case?
- If the case is positively cleared, what kind of IP can Baseclick use to commercialise their invention and why?



Fortunately, BASF was a major shareholder of Baseclick and was big enough to face the US litigation threat. Once its lawyers stepped in, the chances for a balanced agreement looked much better. In the end, the case was dropped and Baseclick was free to continue developing its business.

① Licensing: It is a form of “indirect exploitation” when the IP owner grants others the right to use and exploit its IP, usually in return for remuneration (monetary or other). This is known as licensing. The owner of the IP right is the licensor and the parties to whom it grants the right to use and exploit the IP are known as the licensees. The right to use the IP, together with any specific terms and conditions, is normally granted by means of a legal contract known as a “licensing agreement” (also “licence agreement” or simply “licence”).

The licensor maintains the ownership of the IP right. If the owner sells the IP right to another, then all rights are transferred. Transferring IP is a different strategy from licensing. A licence gives the licensee permission to use certain rights, under certain conditions. Thus, the licensor does not necessarily grant all rights to the licensee.

Types of licences:

- exclusive (not even the patent owner is allowed to use it)
- non-exclusive (comprising more than one licence)
- sole (the owner may use it)
- compulsory (license of right)

(Jeremy Philpott, IP4INNO materials)

② Royalties: Royalties are sums payable for the right to use someone else’s property for the purpose of gain. [...]They are generally paid for the licensing of intellectual property. (Jonathan Law and Elizabeth A. Martin, A Dictionary of Law, Oxford University Press, 2014.)

③ Ownership: The exclusive right to use, possess and dispose of property, subject only to the rights of persons having a superior interest and to any restrictions on the owner’s rights imposed by agreement with or by act of third parties or by operation of law.

[...] A person may be both the legal and beneficial owner, or the legal ownership of property may be separate from the beneficial (equitable) ownership (i.e. the right to enjoy property), as when the trustee owns the legal estate in land for the benefit of another.

A legally valid transaction may confer specific rights to use, possess or deal with property without conferring ownership of it. (Jonathan Law and Elizabeth A. Martin, A Dictionary of Law, Oxford University Press, 2014.)

④ Infringement: Infringement means carrying out prohibited actions such as manufacturing, importing, selling or offering for sale the subject-matter protected by a patent without the authorisation of the proprietor of the patent.

⑤ Injunction: A remedy in the form of a court order addressed to a particular person that either prohibits him from doing or continuing to do a certain act (**prohibitory injunction**) or orders him to carry out a certain act (**mandatory injunction**).

Example: A prohibitory injunction may be granted to restrain a nuisance or to stop the infringement of a copyright or trade mark. Injunctions are often needed urgently. A temporary injunction (**interlocutory injunction** or **interim**) may therefore be granted at a special hearing pending the outcome of the main hearing case. If it is granted, the claimant must undertake or compensate the defendant for any damage he has suffered by the grant of the injunction if the defendant is successful in the main action. If judgment is given for the claimant in the main action, a **perpetual injunction** is granted. (Jonathan Law and Elizabeth A. Martin, A Dictionary of Law, Oxford University Press, 2014.)

⑥ **Standstill agreement:** In a takeover situation, a standstill agreement is an agreement between a company and a shareholder which restricts the shareholder's ability to acquire further shares in the company.

In a restructuring of a company's debts, it is an agreement between creditors (www.practicallaw.com/2-379-0852) to give the company time for information to be collected and for a survival strategy to be put together with a view to establishing a formal restructuring (www.practicallaw.com/1-384-6171).

In the context of limitation, a standstill agreement is an agreement which has the effect of suspending or extending a statutory or contractual limitation period. (<http://uk.practicallaw.com/4-200-4971?service=corporate>)