Project no. 043338

Project acronym: EMERGENCE

Project title: A foundation for Synthetic Biology in Europe

Instrument: NEST Pathfinder

Thematic Priority: Synthetic Biology

Deliverable reference number and title:
D5.1-1/D5.4-1 Workshop Synthetic Biology & IP

Due date of deliverable: Mo7
Actual submission date: Mo23

Start date of project: 1.12.2006 Duration: 36 months

Organisation name of lead contractor for this deliverable: GENEART

Revision [draft]

Project co-funded by the European Commission within the Sixth Framework Programme (2002-2006)		
Dissemination Level		
PU	Public	
PP	Restricted to other programme participants (including the Commission Services)	
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Workshop Synthetic Biology & IP

June 16, 2008, 10:00 am – 3:00 pm, Munich TUM

GENEART as one of the industrial partner within the EMERGENCE Initiative responsible for the interface of Academia and Industry, organized in collaboration with ETHZ a workshop at the Technical University of Munich (TUM) on June 16, 2008 in the line of the work package mission to built a conceptional framework for the integration of the European industry in the development of Synthetic Biology. The participation of industrial stakeholders is regarded an essential step for a sustainable development of this emerging discipline. Accordingly, the goal of this workshop was to develop a recommendation, in a round of experts, on an IP strategy which is suited to promote this process. The interdisciplinary circle of participants consisted of experts in the field of technology and innovations management (J. Henkel, T. Fischer & F. Jell, TUM), patents in the industry (K. Schwander, DSM, C. Ludwig, Geneart) and of the publicly regulated patenting process (B. Rutz, EPA), academic and industrial application developers (S. Panke, ETH, L. Pasamontes, DSM) as well as commercial service providers (R. Wagner & F. Notka, Geneart). Focus of the workshop was the discussion of the opposing model concepts on the use of shared resources "open source" (sharing) and "incentive-driven networking" (patenting) regarding the willingness of the European life science industry to participate in the development of the field of Synthetic Biology.

As an introduction into the history of the development of Synthetic Biology, which is tightly connected to establishing the first open source platform in the field of molecular biology and biotechnology, S. Panke provided an overview of the projects "Registry of standardized parts" and "iGEM-competition" developed at the MIT.

In 2004 the "Registry of standardized parts" was introduced at MIT with the goal of the students' early integration into the practical laboratory experience of biotechnological work. At the same time, interdisciplinary approaches in the areas of synthetic chemistry, biotechnology and engineering were to be promoted. Starting in 2005, those goals were complemented by holding the inaugural "iGEM competition". Those summer school projects for students of various faculties take advantage of accumulated and archived parts of the registry to conceptualize their own ideas, construe respective models and acquire hands-on experience.

Standardization is thereby a requirement to i) allow modular utilization of an application, but furthermore to also ii) do justice to a (still) visionary, automated production. In order to expand the registry as an open source platform, the participants are required to reposit the parts developed, while – in the strict sense of a genuine open source policy – the distribution of parts takes place without any contractual obligations (MTA). Early drawbacks of these initiatives definitely reflect other open source movements with an uncontrollable exchange: the functionality of bio-bricks is very limited. Furthermore, the parts are currently only available to students. This parts library lacks IP-relevant information entirely.

Questions on the open source concept arise with respect to legal certainty as well as to innovation: Is an MTA necessary? Is a disclaimer required? Would automated search engines that indicate a breach make sense? How can gratifications for innovative contributions be introduced?

If the open source solution is compared to an IP-based solution, which as per definition restricts free access to the parts, the question arises if a legal system can be drafted, which allows uncomplicated handling (internationally as well). However, active contribution needs to be encouraged in an IP-based model as well (i.e. is a bonus system based on user frequency to increase motivation conceivable?).

Advantages and disadvantages of both concepts (open source vs. IP-based) were outlined in an overview by J. Henkel.

With respect to an open source based solution, the following essentials were presented and potential directions and problems of development were outlined drawing analogies to other open source concepts: The idea of non-restriction in an emerging field is, from experience, only transient. Regulations would necessarily arise while establishing a system. Hence, identification of patent-relevant parts would make sense from the very beginning. As a potentially negative progression the tendency of network effects was pointed out. A “lock-in” effect (accustoming to something used repeatedly) is to be expected for parts as well. To the degree that scientists exchange knowledge on parts, these (individual) lock-ins result in network effects and tend to lead to a collective lock-in. This means favouring previously/often used parts without the respective qualitative evaluation (winner-take-all trend). Examples for lock-in effects can also be found in current research. Network effects in biology when using cell lines for example can be measured by recording the cell lines (and their equivalent counterparts) used in publications like NSCB, ATCC, etc. It is likely that “sets” of parts exist in Synthetic Biology, which are compatible and complement each other. The possibility of “tipping” and “winner-take-all” results then apply to these sets as well. Competitive situations occur between these sets where certain parameters like lifecycle costs (royalties), risk, transaction costs or investment costs have a direct effect on their success. Hereby the successful set may very well be proprietary.

On the other hand open (and to a certain extent also selectively open) systems may definitely be profitable.

Approaches occur on part of the IP-culture that may mitigate property rights impeding open development. Thus, commercial patenting of tools shows a declining trend and due to easier enforcement, patents are rather limited to relevant areas (technologies and products). In addition licensing of minor improvements is usually costly and technology infringements would be difficult to detect anyhow. The problems of the patenting situation in the Asian region appear to relax as well. The Chinese patent system for example has significantly improved (as well as the legal system in the course of a convergence to Western standards). Although this is not true to the same extent for India, positive trends can also be observed here. The open source solution has already proven to be profitable in other areas (i.e. embedded Linux: profit by open source: on average approx. 50% of the code is released).

Additional arguments supporting open source, which could be based on strict copyright regulations instead of on the protection of IP with patents, include the promotion of technological advancement (informal collaborative development). For example, the option to set a technological standard or an alternate development (with innovative character) is encouraged as a strategy to bypass protected solutions. Furthermore, the modularity of the system facilitates a selective “evasion”, which may additionally be supported by identifying IP-relevant parts. Not to be underestimated is also the side effect of a contribution (marketing effects, visibility, reputation).

However, patents currently perform important functions, which argument against an IP-free open source: patents are needed for VC investments, and industrial cooperation is often based

on a “culture of patenting” which thrive on cross licensing agreements. “Traditional” IP protective mechanisms are also generally (but not always) important to reap profits from innovations and to justify respective development costs.

Subsequent to the comparison of pros and cons of an IP-based open source solution, B. Rutz presented potential scenarios for a Synthetic Biology-related IP solution.

Two documents are relevant for patent issues on the European level. On the one hand the EPÜ2000 which admittedly regulates the patenting in accordance with the European Patent Convention, but covers the consequential use of patents like licensing, infringement and invalidation procedures (national law) only to a limited extent; on the other hand Directive 98/44/EC as a guideline of the European Union for patenting biotechnological inventions. Various search options are available for patent enquiries, i.e. patent databases (espacenet, epoline, register plus) or patent sequence databases (EBI for US, EP, JP patents).

For the use in own developments the research exemption is a very relevant topic in dealing with IP-attached parts, especially since very non-uniform legal systems exist for licensing, registration and approval. In contrast to the U.S., which permits only philosophical research, most European countries allow research **of** but not **with** patented inventions; while several countries have implemented special provisions. Switzerland, for example, has non-exclusive licenses for research tools and Belgium offers an extended option for compulsory licenses for biotechnological or health-related inventions.

As hot topics in regard to patenting issues, the demand for freedom of research, the observance of ethical concerns and morale, the topic of bio safety and bio security as well as problems related to patent trolls/sharks, blockages, thickets and the incurrence of commons/anti-commons were named.

With respect to dealing with IP, no significant differences appear to emerge between Synthetic Biology and biotechnology at first glance since results/products are largely identical. However, if the development is considered significant differences do emerge, which go back to complexity (cf. micro-arrays with many defined and patented parts), interconnectedness (the functionality is derived from combinations), and interdisciplinary (links to chemistry, computer science, electronics, nanotechnology).

If all factors mentioned are included in the potential development of the Synthetic Biology, differing scenarios can be constructed depending on how individual parameters are weighted. Four of those scenarios were presented (SB Scenarios 2025)

1) The model ”Market Rules“ is dominated by business-driven development. The patent system is harmonized on a global level and innovations protected by patents dominate. Cross licensing and arrangements between established players impede the market entry of newcomers.

2) “Whose game?” is dominated by geo-politics. Regional patent systems have evolved and established themselves in this model, where IP rights are state controlled, which inhibits global implementation. The TRIPS Convention fails here.

3) “Trees of knowledge” delineates a socially driven system in which patenting is largely abolished and Copyright is restricted. Development is based on open source networks directly boosting research. Non-disclosure of innovations is characteristic as is an increasing political influence and lobbies resulting in innovation gaps in “sensitive” areas.

4) “Blue Skies” is mainly driven by technology. An increasing IP blockage in complex technologies results in long-winded application processes, which in turn collide with the

increasing demand in technology. When dealing with complex products with numerous IP holders, problems occur regarding the clarification of rights. The result is a split of the IP system by type of technology into license-of-right regimen for complex technologies.

After the presentation of various aspects of IP and open source topics from relevant areas such as science, economy and regulation, tangible approaches for dealing with IP and establishing of a European SynBio network were openly discussed.

From the industry's point of view various scenarios are conceivable for successful development options. The goal should be to find a feasible system which facilitates a preferably large access across a broad front.

In the field of science a general policy on the access to reagents/information with the goal of sharing already exists today. Initially, pertinent research results are legally protected (through patenting), made publicly available in publications and saved databases as searchable information. Basically a publication obligates sharing. However, practical experience shows that an MTA (Material Transfer Agreement) is exchanged for legal protection, which can be freely drafted as a contract and provides the inventor with the opportunity to pursue his/her own goals and delay developments of others.

In addition to this police, an open source scenario would offer advantages that would contribute significantly to a faster development. Apart from immediate availability of reagents (which is the bigger issue), especially the introduction of an industry-standard is viewed as important progress. Not only the standardization of parts (for simpler utilization analogous to electronic circuit diagrams) but in particular the availability of standardized and high-quality specifications for process steps like analysis, documentation, handling or shipping was emphasized (examples for standardized databases are AIDS Research and Reference Reagent Program (NIH), Gateway (Invitrogen), Geneglobe (Qiagen)).

For dealing with IP protected components, two options generally exist: open source excluding patented parts (freedom to operate status) or identification of patented parts (necessitating an IP regulation).

Both models deal with the issue of the patent status's uncertainty. Various approaches suggest on the one hand the obligation of the provider of the part to document the status or to collect the information in a database and to adequately link this information as Wikipedia does. The identification of patented parts would in any event allow a user to prevent utilizing IP.

However, the exclusion of patented parts is associated with negative effects. Lock-in issues may result in the definition of non-optimal parts as standards, which shut out "reasonable" developments (and their reuse). Also, the interest of potential industrial developers is questionable without patent protection and hence, without the active creation of net value. This is offset by the respective administration expense and legal arrangement, which become necessary with the integration of patented parts. A feasible compromise would be a release in various categories. "Small" parts, with a low priority for companies, could become freely accessible (at least for R&D), while protecting complex systems including experimental data ("pain threshold") by the industry would be absolutely essential. Legal protection would require the institution of an obligatory MTA standard, which, however, should be defined within the network such that the administrative expense is limited (quick processing without red tape). Furthermore, it needs to be ensured that sufficient information is available on existing IP, that the number of contributors (parts manufacturers) is sufficiently large and that the contributors are bound to reapply their experience/advancements based on those parts. The availability of information on inventors (reputation) and on the parts made available would support this concept. In this context, disclosure (patenting/publication) and open source

generally provide the same information. However, the information made available by disclosure is complex and unstructured, i.e. it lacks a functioning and uniform information management system (standardized search), which could be established in an open source set of rules. The complexity could be limited while increasing the integrity by introducing even a partial standardization and a concentration (i.e. limiting of regulatory elements and certain systems like E. coli/yeast and CHO) is implemented. “Natural growth” would expand such an information system due to demand.

An issue with respect to the availability of parts pertains to the necessity of a registry: is the structure and accessibility of information (database) sufficient?

Standards in the gene synthesis sector already exist today in the areas of production (incl. design and bricks principle), analysis and QC. The allocation of standardized parts and complex modular “circuit diagrams” is possible for industrial providers as well.

Requirement for financing arise as well from an open source solution. A turn-key open source system including registry requires a link to and the commitment of funding agencies (for the promotion of a public exchange and the formation of networks).

An incentive perspective (win-win situation) needs to be developed to include the industry, to promote contributions to the registry. Thereby an arrangement for linear developments (2 partners) would be fairly simple. For complex developments (see patent thicket computer) various strategies are conceivable. Patent pools, open standards, cross licensing and commons are among those approaches that are already being successfully used. The Cambia BiOS Initiative (Australia, Richard Jefferson, IP sharing within “commons”) and the “Joint Research Center for Standardization” were suggested to evaluate the various strategies.

The conclusion of the workshop can be summed up such that the realization of a European registry is feasible and that IP relevant parts should not be excluded. Essential requirements are i) the introduction of a standard MTA and ii) an information management platform as well as iii) the integration of funding agencies.

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