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# ROCK: the Roche medicinal chemistry knowledge application – design, use and impact

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**Medicinal chemistry is a complex science that lies at the interface of many fields of research and at the very heart of drug discovery, with property relationships based on chemical structure at its core. It is clear that the effective capture and dissemination of medicinal chemistry knowledge and experience will be a key differentiator among pharmaceutical organizations and crucial for the future success in delivering effective and safe drug candidates. Therefore, in 2005 we developed ROCK (Roche medicinal chemistry knowledge), an internal user-friendly and peer-reviewed Wiki-like application to capture, browse and search tacit knowledge, key discoveries and property effects related to chemical structure, which is used as a primary source for addressing challenges faced in drug design.**

Medicinal chemistry lies at the interface of many fields of research at the very heart of drug discovery, with property relationships based on chemical structure at its core. A successful drug-hunter requires a good grasp of an ever expanding knowledge pool across multiple domains related to chemical structure, such as molecular properties, pharmacokinetics, pharmacology, structure-based design and toxicology. Naturally, such knowledge is built up over time and is greatly influenced and even biased by personal experiences gained in ongoing projects in various stages of the preclinical discovery phase and disease areas. It is this invaluable tacit knowledge and experience that is most difficult to make explicit and transfer between scientists, and, in particular, to new generations of medicinal chemists across multicenter organizations. Despite decreasing cycle times, medicinal chemistry programs can still last up to several years, and the number of projects and target classes an experienced researcher is exposed to, even over a decade of research, is limited. Insights gained over the years can be quickly lost or overlooked and are, thus, often not readily accessible to other members within modern-day global research communities.

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## Tacit versus explicit knowledge

The concept of tacit and explicit knowledge is one of the most important principles in organizational learning as part of strategic knowledge management. First introduced by physical chemist and philosopher Polanyi [1], tacit knowledge describes highly personal, often context specific, subjective insights, intuitions and hunches; whereas explicit knowledge is systematic, codified and formal, and can be easily communicated and shared in the form of 'hard' data. According to Nonaka and Takeuchi [2], organizational learning can be described as a process of interaction and alternation between these two knowledge types. Tacit knowledge can be made explicit by being codified in manuals or incorporated in processes. The reverse event is the interpretation of explicit knowledge using an individual's frame of reference which can become tacit knowledge. Together with sharing of tacit knowledge and dissemination of codified knowledge these processes are the basis of increased access to knowledge and the enabling of decision making in companies.

Making use of individual tacit knowledge and transforming it into explicit knowledge that can be stored and shared much more easily has become a crucial success factor for the pharmaceutical industry. It is widely accepted that the majority of an

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organization's knowledge base resides inside the heads of its employees [3]. If not appropriately captured it is easily lost through organizational changes, employee reassignment or project outsourcing and terminations [4]. Although explicit knowledge is used to guide the way the daily tasks are organized, it is tacit knowledge that often has a fundamental role as the driving force for creativity and innovation [5].

Further to managerial support and a lively knowledge sharing culture, the available technology is an important factor in collecting and codifying knowledge for further distribution. A reliable, user-friendly and cost-effective IT framework is regarded as a key enabler for this process. Despite the increasing number of public online tools and systems for knowledge sharing, for many sectors of industry this infrastructure is not available off-the-shelf for internal use and has to be developed and maintained by the company [6,7].

## Challenges of sharing medicinal chemistry knowledge

A generally accepted model to explain the difference between knowledge and data is the traditional knowledge pyramid as originally proposed by Ackoff [8]. The concept describes increasingly higher levels of abstraction starting with data (the basic facts, 'what'), leading to information (processed and structured data, 'know-what'), evolving further into knowledge (contextual and applied information, 'know-how') and ultimately culminating in wisdom (applied knowledge and evaluated understanding, 'know-all') (Fig. 1).

The importance of effective knowledge management in the pharmaceutical industry is undoubted, because a vast amount of data, information and knowledge is created by many individuals for every research project. Whereas the storage and 'searchability' of data or information, such as biological data, lab journal content, project and business reports, are generally well established, it is often challenging to retrieve the experience (knowledge) relating to how a specific research problem was solved in detail or why a certain decision was made.

As far as medicinal chemistry is concerned most of the knowledge, be it explicit or tacit, is of course centered on chemical structure. Most of the available tools for knowledge sharing, like Wiki-based systems in 2005, were not particularly suited for comprehensive structure or substructure queries nor were they readily interconnected with primary internal data warehouses [9].

At Roche there was an increasing need to share explicit and tacit medicinal chemistry knowledge in a simple way, ultimately leading to the design and implementation of a custom-made application in 2005. The aim of the tool was to allow the capture and dissemination of knowledge relevant to structure–property and structure–activity correlations to enable prospective drug design (problem anticipation and avoidance) and retrospective analysis (problem solving). It was decided deliberately not to include technical aspects such as compound synthesis or handling – to focus on medicinal chemistry drug design concepts. Although several knowledge sharing platforms relevant to medicinal chemistry, such as proprietary Wikis or public blogs, have recently been reported [7,9,10,11], to our knowledge no such described application accomplishes all the tasks available with ROCK (e.g. sharing specific examples of summarized and interpreted results on specific categorized topics, compounds or projects).

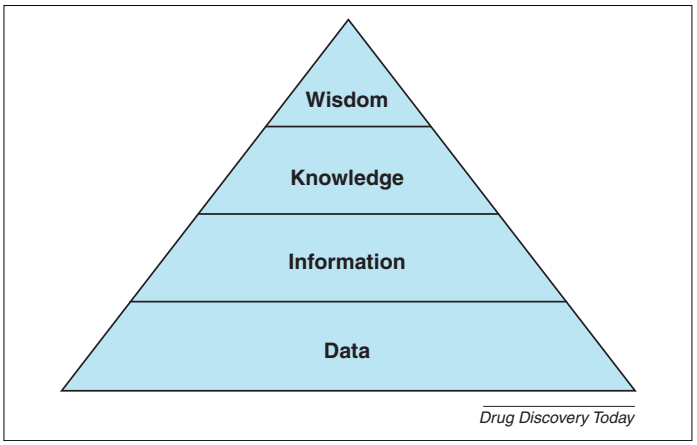


**FIGURE 1**

The knowledge pyramid. The DIKW (data–information–knowledge–wisdom) model is illustrated here.

## The ROCK application

As the basis of this knowledge management tool we defined the 'knowledge slide', the PowerPoint® slide that is submitted by the author on a certain topic with medicinal chemistry relevance. The main author is usually the synthetic or computational medicinal chemist who has made a noteworthy observation or a specific analysis; other project team members that contributed to the solution or finding are listed as co-authors. There is no fixed format for this slide to allow for creative freedom, but the slide should capture the knowledge in a highly graphical and concise format. In many cases, only minimal effort is needed to extract this slide from an existing presentation, which lowers the motivational barrier for submission. As a result of the open and flexible format the tacit knowledge of a medicinal chemist can be captured in any form – be it experiences from internal projects or insights based on sources from the public domain, which might not be retrievable in a straightforward way using commercial or public tools. To ensure the collection of knowledge rather than data, authors are asked to explain correlations and results, and to draw conclusions that could have the potential for broader or general applicability (Fig. 2).

For the application the following requirements and features were defined:

- the tool is a web-based application,
- viewable in a graphical abstract layout,
- readable as a book organized hierarchically through categories and subcategories,
- searchable via keyword and advanced text search,
- searchable via substructure searching,
- the knowledge database is created by all chemists via an online submission feature,
- the database is continuously updated and expanded,
- the application includes and online editor functionality to enable fast review and categorization of the submissions.

After careful evaluation of various options it was decided that an in-house Wiki-type application with particular additional features and functionality would fulfil the requirements most effectively. A three-tier architecture with an underlying database, an application server with the business logic and a web interface were implemented.

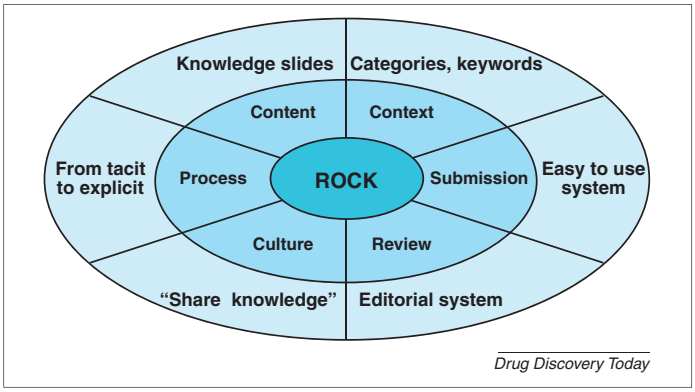


**FIGURE 2**

Strategy and content of the Roche medicinal chemistry application.

This approach had the additional advantages that other in-house systems, such as the user directory and the compound database, could easily be integrated and links to ROCK knowledge entries could be added into global data sharing applications.

In addition to a field-based advanced search interface (Fig. 3) a simple global text search was implemented. In the search result the matching text strings are highlighted and the results can be further filtered by author, publication date, research site or status. A substructure query searches the content of the entire Roche compound database and intersects the search result with the compound identifiers associated with the individual knowledge slides. These two simple search types can be combined providing a very powerful yet easy way to find relevant chemistry knowledge.

To ensure quality, it was decided that new knowledge submissions undergo a brief editorial review process before publication with the goal of optimizing layout and the clear description of the content with key messages to maximize impact across the community (Fig. 4). An additional editorial task is to review the categories and controlled vocabulary for the keywords to optimize consistency and 'searchability'. Owing to the global scope of the knowledge database and to allow close contact with the authors, the editorial team consists of 2–4 scientists at each research site. These local teams meet regularly to discuss the recent submissions and to manage change requests and entry updates.

ROCK features an easy-to-use online submission form for entering the metadata comprising fields for author name, co-authors, title, abstract text, full text, project identifier and a list of compound codes as well as upload features for the knowledge slide PowerPoint® file and the graphical abstract. Categories and keywords are selected via a pop-up menu with controlled vocabulary. Supplementary information from the public domain, for example from journal articles, can be included in the abstract and full text fields and accessed directly via hyperlinks to the publisher's website through a document (doi) or PubMed (pmid) identifier. Special emphasis has been put on the definition and handling of slide status to cope with the editorial review process. Depending on the user role (i.e. author or editor) and the status of a slide the action that a particular user can perform is clearly identified and no selection of a particular user role is needed upon login to the application.

A hierarchical tree of topics allows intuitive browsing. Five main categories were defined: biology and pharmacology, DMPK,

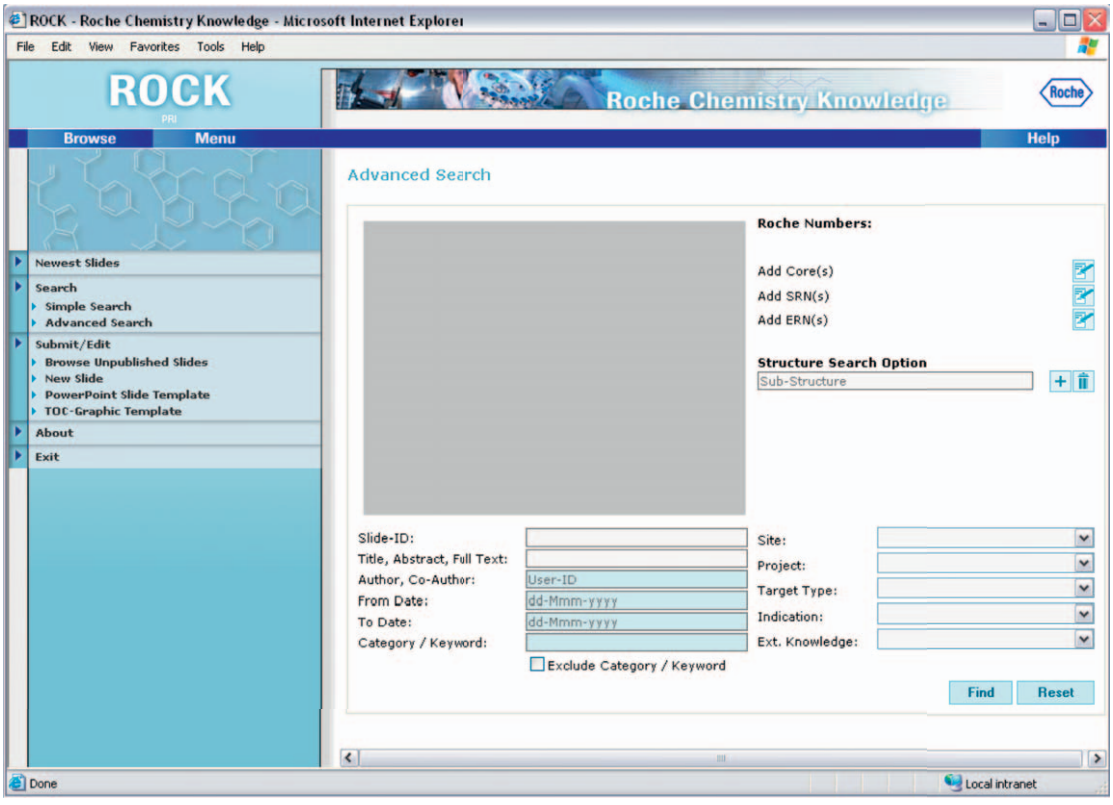


**FIGURE 3**

The advanced search function within ROCK.

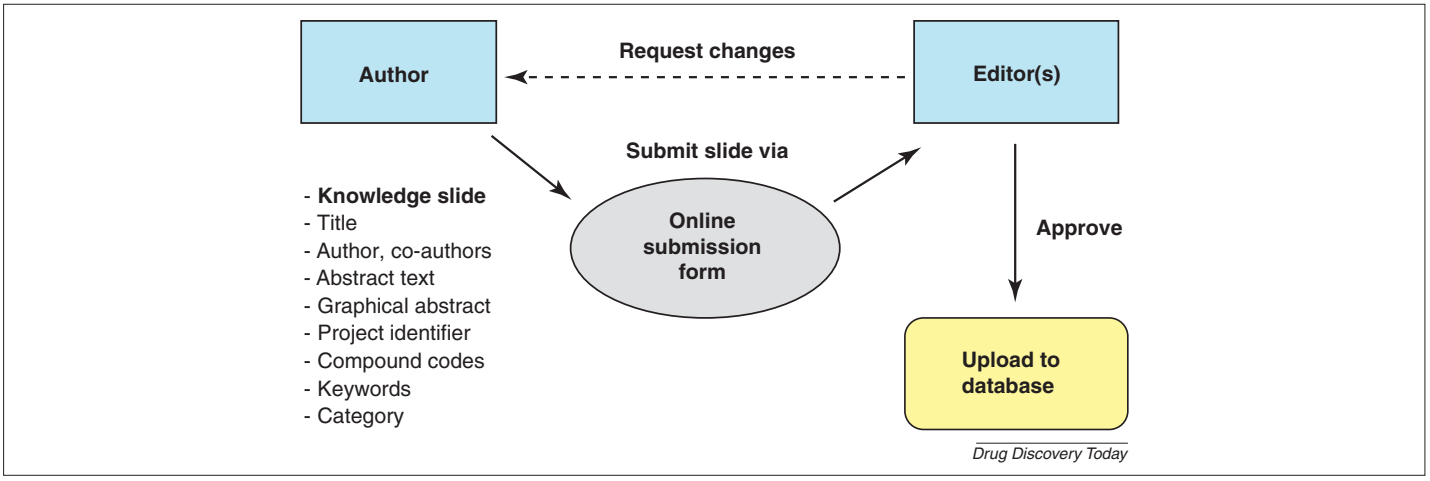


**FIGURE 4**

Knowledge slide submission and editorial process.

physicochemical properties, safety and structure. More recently the category: 'presentations and seminars' has been added to the system. In this new category entire medicinal chemistry presentations are uploaded. Hyperlinks point to additional knowledge slides on which specific findings have been elaborated in more depth.

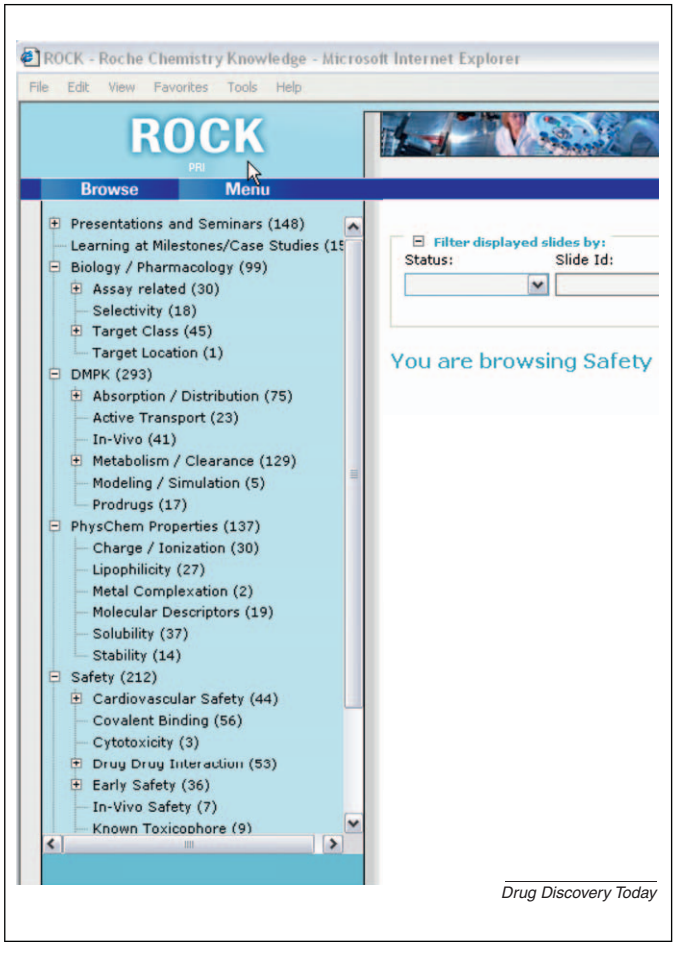


**FIGURE 5**

Screenshot of the ROCK application showing the hierarchical tree of categories and subcategories.

Each of the main categories is further divided into several subcategories in one or two levels that can be collapsed or expanded in the 'browse' view (Fig. 5).

By clicking on the name of a category or subcategory in the hierarchical tree a list of respective knowledge slides is displayed in a summary layout (Fig. 6). This summary contains the essential fields and key messages, such as title, author, graphical abstract, abstract text, categories and keywords. Another mouse-click opens the underlying PowerPoint® knowledge slide or the full-text view including more-detailed information on the project and the compounds shown (Fig. 7).

To emphasize the multidimensional nature of the knowledge captured, each entry can be assigned to multiple subcategories (e.g. a slide on the lipophilicity–hERG relationship is assigned to the categories 'physchem properties/lipophilicity' and 'safety/cardiovascular safety/hERG'). In addition, knowledge slides can be linked to any number of related slides. The editors deliberately abstain from biasing the content of a newly submitted knowledge slide. Thus, subcategories can contain multiple entries covering similar or opposing observations, which might allow conclusions across these examples on the degree of generality of a finding. An example would be the impact of modulating 'basicity' on the potential of compounds to block the hERG potassium ion channel.

## Present experiences

The initially defined ROCK strategy (Fig. 2) proved to be very successful. Since its launch ROCK has accumulated close to 900 distinct knowledge slide entries covering six main categories and 70 subcategories. It is used by hundreds of chemists every month across all of the global research sites and is playing an important part in solving medicinal chemistry challenges while continually educating the Roche community. The intuitive use, such as 'simple searches' for text field searching, and the possibility to combine text and substructure searches are appreciated most by the chemists. Further, the application allows the display of the 20 most-recent entries after login as well as email alerts, which are useful for getting updated on new findings.

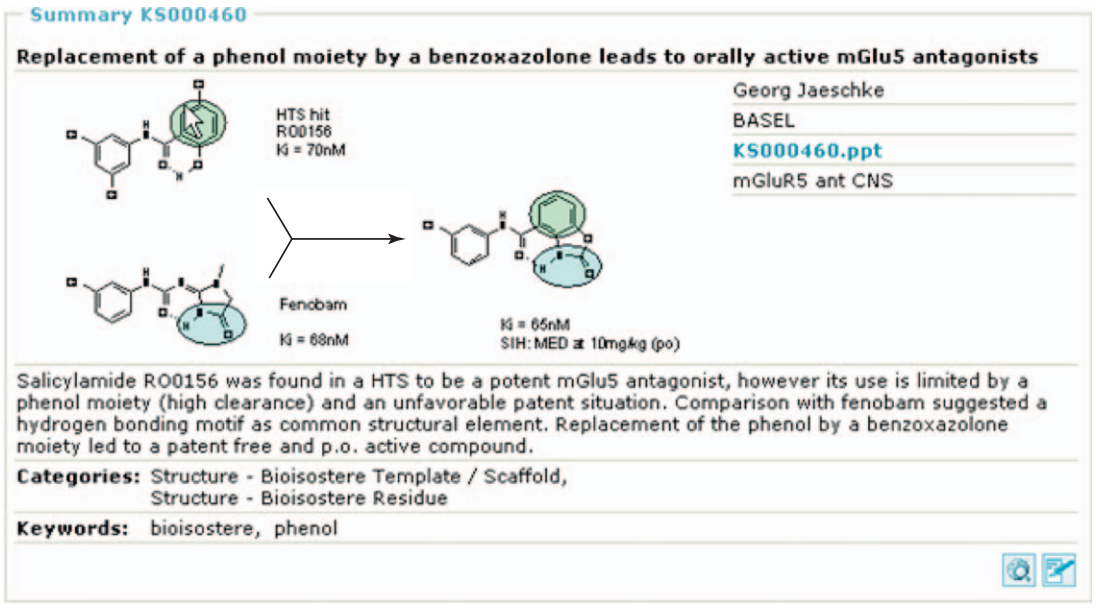


**FIGURE 6**

Summary layout: abstract view of a knowledge slide.

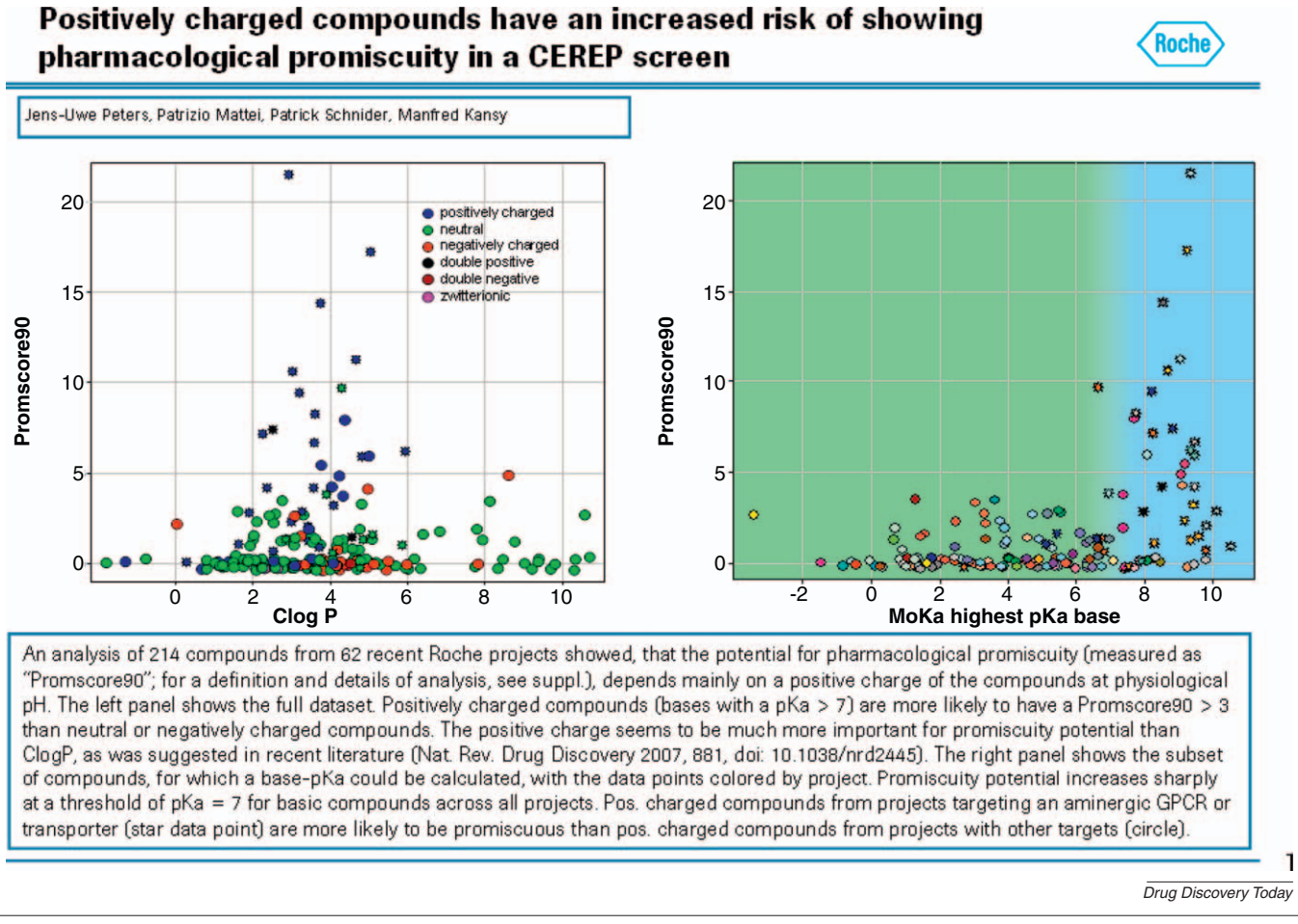


**FIG. 7**

Full PowerPoint® slide: knowledge slide providing more detail on a captured entry.

ROCK plays an important part in maintaining an open knowledge-sharing culture and the value of the collected tacit and experience knowledge is highly rated. Contributions to ROCK are acknowledged and management has always been very supportive to this project. Studies have shown that reward and recognition are particularly important factors in sharing tacit knowledge, because of the traditionally higher hurdle in bringing such knowledge into a shared medium [5,12].

Furthermore, close contact between the editors and chemists is valuable because this allows soliciting of key contributions after internal presentations or meetings, to collect findings in a timely manner enabling a continuous flow of submissions. When new knowledge is generated concerning an existing slide, this slide can be easily updated by the author via the usual submission process. However, a systematic update is not requested because ROCK is designed as a more permanent collection of individual cases of medicinal chemistry experience that might not necessarily be universally generalized.

Finally, easy access and integration within other scientific information systems are of high importance and, thus, ROCK entries are accessible via direct links from other internal applications and databases where biological or physicochemical data are stored and managed. It has become common practice to include the slide identifier numbers in formal internal medicinal chemistry reports and project updates.

With many ROCK categories richly filled with entries linking numerous other categories, the accumulated knowledge can now be used as a primary source for general reviews on topics or challenges faced in drug design and medicinal chemistry.

## Concluding remarks

The effective capture and dissemination of knowledge and experience related to chemical structure are crucial for the future success of pharmaceutical companies. Tacit knowledge is especially difficult to access and is paramount for creativity and innovation. To help harness this asset, user-friendly knowledge capturing tools not only provide access for the organization but also support and foster knowledge sharing as an integrated part of the research culture. For this reason we feel that ROCK will assist to capture, browse and search knowledge related to medicinal chemistry continually. Owing to its highly structured, verified content and extensive searching capabilities, including substructures, ROCK has gained high acceptance within our company among scientists globally.

## Conflict of interest

The authors are employees of F. Hoffmann-La Roche Ltd.

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