

*My greatest satisfaction has come from knowing that our efforts helped to save lives and relieve suffering. When I was baptised, my father held me up and dedicated my life to the service of mankind. I am very proud that, in some measure, I have been able to fulfil his hopes.*

**George H. Hitchings**

# editorial



**Joost C.M. Uitdehaag**

## Where is the optimism? Warrior teachings to regain the drug discovery spirit

During the drug discovery session of the American Association for Cancer Research Meeting 2006 (<http://www.aacr.org/>), something peculiar happened. After the talks, the first question was not about the content, the difficulty of finding good compounds, the legacy of high throughput screening, or the persistence of the productivity decline; instead, the first question was 'But where is the optimism?'.

This remark described the atmosphere in the drug discovery session. And it awoke in me, and perhaps in many others [1], a

slumbering suspicion that a collective depression might be bothering the pharma industry. Perhaps we are starting to lose faith in drug discovery, thus making R&D productivity decline a self-fulfilling prophecy. And perhaps, it is now time to start studying the decline more from a psychological perspective, and to start looking for ways to lift ourselves up, mentally.

### A depression and its origins

Is there a depression in pharma? The classic symptoms of depression are: feelings of pessimism, helplessness, irritability, difficulty in making decisions and loss of energy (<http://www.nimh.nih.gov/publicat/depression.cfm>). Some of these feelings are reflected in recent reports on R&D practices in the pharma industry [2–6]. For a more objective measure, I tried some quick Googling. These are data from 4 Sept 2006: In general on the web, 'industry + optimism' gets 4.1 times as many hits as industry + pessimism. But 'drug discovery' + optimism only gets 3.5 times as many hits as 'drug discovery' + pessimism. This makes the drug discovery positivity ratio  $3.5/4.1 = 0.85$ . For the pair confidence–depression, the positivity ratio is even as low as 0.07. Compare this to 'information technology', which scores 1.5 and 1.9 on both ratios, respectively; or 'car industry', which scores 7.8 and 1.3. Pharma appears to be more depressed than even the notoriously turbulent car industry.

I can imagine where the depression comes from. My generation has had to deal with birth defects caused by thalidomide and with housewives addicted to tranquilizers. My generation was taught to distrust big pharma (actually large companies in general) and to favour the benefits of alternative medicine. And the pharma scandals continue. When students visit me, their first questions are about animal testing, unaffordable drugs and neglected diseases. These are good questions, but are not about drug discovery. Drug discovery is not a profession held in high regard, as witnessed by the 2510 Google hits for drug hunter (on 4 Sep 2006), and the 792 for drug discoverer, compared to the 316,000 for forensic expert, and the millions for rocket scientist, diplomat or carpenter. Even companies support the negative image: boasting in a masochistic manner about their horrible attrition rates and massive costs [2] and telling me that I have only a tiny chance that I will see a product hit the market, but a good chance of seeing a good drug shelved because of management decisions. It is hard to imagine anyone can believe in drug discovery nowadays.

## Sources of inspiration

Thus, how can we bring back the optimism? There might be many ways towards this [1–6], but I would suggest to start with ourselves, because perhaps a bit is due to us being too complacent and arrogant on one hand, and too afraid on the other hand. Let us listen to two complete outsiders, management trainers, who I once overheard talking about pharma researchers. They found drug discoverers were surprisingly sceptical about their jobs. Drug discoverers seemed to think nothing would ever come out and nobody could do anything about it, whereas the trainers expected drug hunting to be one of the most rewarding jobs in the world. After all, is drug discovery not about curing people? Is this the feeling that we need to reinforce?

I suggest going back to our roots to discover the confidence that drove the likes of Florence Nightingale and Albert Schweitzer and which also drove drug-discovery giants such as James Black, who did not do a PhD but won a Nobel prize, with Gertrude Elion and George Hitchings, for drug hunting, or Paul Janssen, the Belgian gentleman and hors catégorie drug hunter who made it to the market with only his fifth compound. The passion and motivation of these people can be found in their texts, amid the steaming frustration about present-day working practices [7–10]. These people seemed to have had an inner belief that they were doing a good thing, something which helped them to stay on track and gather support, free of helplessness or indecisiveness.

## Musashi

How could we get this feeling back? We could use an inspirational text by a successful veteran. A kind of code just to keep us confident and convinced, even in the darkest times. For this, I suggest digging even deeper into our roots, and appealing to our professional ancestry as warrior-hunters. We often invoke them by using the term ‘drug hunters’ or ‘the war on cancer’, or by using combat talk in drug hunting editorials [10].

To gain inner strength, warriors refer to codes. One of the most famous surviving codes is the *Book of the Five Rings*, by Miyamoto Musashi, the legendary samurai who emerged victorious in 60 duels [11]. Musashi mixed zen philosophy and martial strategy into principles that are useful for anyone who wants to be victorious or successful. He is increasingly popular today, with four million Google hits. The field of general management has used his book extensively [12]. At the start of his book, Musashi states nine principles (which can be downloaded as a free screensaver from <http://artofwar.thetao.info/software/index.htm>). It is exciting to find that these principles significantly overlap with the working practices of the drug discovery giants [7–9]. Therefore, I suggest mixing both sources into a new Musashi code:

### A Musashi code for drug discoverers

#### *Do not think dishonestly*

Truly desire to discover a drug. This translates into the commitment that Black saw as being essential in Janssen [7]. Do not secretly desire to be a famous scientist, a general manager or a technical expert. Do not secretly strive for recognition or status. Work only for one reward, that is, to know you join with others to combat disease. Only then you will be able to persevere against all setbacks, and be a true project champion. As Musashi says: ‘Even if

you strive diligently day after day, if your heart is not in accord with it...this is not a genuine path.’ [11].

#### *The way is in the training*

Constantly seek to improve your drug-hunting skills. Drug discovery is not merely a game of chance, it is something that one can master, as was proven by the old giants. It is about skills in life sciences, but, as in a true hunt, also about experience and intuition. We can learn such values from old and modern stories about drug discovery. For this, we need to cultivate the drug-hunting tradition. We need to tell each other project stories at conferences and meetings [13]. We need practice and mentorship, by getting involved early in our careers in drug discovery projects.

#### *Become acquainted with every art*

Get a feel for all the disciplines that are needed for drug discovery. Develop an area of specialization, but also have working knowledge of the other research expertises. One discipline will never tackle a project, and the combination needed will vary constantly. You need to be able to assess the proper combination. As Janssen says [9]: ‘the various disciplines are like fingers of a hand: of the same origin, but no longer in contact. It requires perspective, deep understanding of the problems to be solved together, enthusiasm and above all motivation.’

#### *Know the ways of all professionals*

People outside drug discovery, such as lawyers, academics, marketers and government officials, will often surprise you with their different way of thinking. Try to understand their reasoning and their logic, because this will help you overcome resistance to your project, now or in the future. Consider Musashi’s words: ‘even if they’re not your path, if you have wide knowledge of the ways, you encounter them in everything.’ [11].

#### *Understand the harm and benefit in everything*

Consider this when, for instance, mobilizing new technology, applying for extra budget or head count or forcing deadlines. None of these things are inherently beneficial. It will all depend on the context of a project at any given stage. Dogmatism in peripheral issues will lead away from drug discovery, which is not the true way. Black’s comment ‘nowadays, we’re obsessed with techniques,’ fits in here [8]. Musashi’s point is: do not try to win with a certain strategy, try to win any way you can.

#### *Learn to see everything accurately*

Conceive the entire trajectory. Musashi makes much of developing a bird’s eye view free of personal biases. This view will help you to adapt to changing circumstances most quickly and efficiently. It will also help you with an objective perspective on pet projects. Black calls it concentration [7]: ‘Concentration is necessary to allow the evolving complex picture to be clear in the mind so timely judgments can be made about when to continue a line of chemical thought and when to change direction.’

#### *Perceive those things which cannot be seen*

A quote on Janssen suffices ‘Dr. Paul never started a project without a conception in his head, a conception that not only specified a

chemical starting place, a 'lead' molecule, with appropriate bioassays but also embodied foresight of how his invention would deliver clinical utility. [...] The creative act of invention is to judge when the product is 'fit for its purpose'. Good judgment comes partly from experience, partly from imagination, and partly from a kind of aesthetic intuition. Dr. Paul was endowed with all of these qualities." [7].

#### *Pay attention even to trifles*

Clinical trials have gone wrong because of a slight difference in formulation. As we all know, the discovery of penicillin began with a forgotten culture plate. This illustrates a general principle. Musashi's opinion is that the large-scale, the general trend of a project is easy to understand because it moves slowly. However, the small-scale, the detailed, moves quickly and so confuses us. But this is the uncharted territory that hides the breakthroughs [11].

#### *Do nothing which is of no use*

Do only things that will lead to decisions or experiments that will bring a drug closer to the market. Do nothing because 'it's nice to know', or to please other people, or yourself. Do not get involved in everything, but focus so as to do one project well, and become its champion. Do not get distracted or demotivated by more rapid advances in other projects. 'Once Dr. Paul got his mind on a new concept, he never gave up on it.' [7]. Instead, consider Musashi: 'As far as speed is concerned, the question of fast or slow in anything derives from failure to harmonize with the rhythm. When you master an art or science, your performance does not appear to be fast.' [11].

#### **Conclusion**

How can we bring these old warrior's philosophies alive? I would suggest remembering them, try to fit them into our projects and to

mirror our daily activities in them. In this way, we will bring drug discovery back in the spotlight. And by knowing that we are following a true path, we will gain a new confidence, which will be a foundation for renewed success. By doing so, perhaps one day drug hunters will be known for their inner strength and uncanny optimism.

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## **Free journals for developing countries**

The WHO and six medical journal publishers have launched the Health InterNetwork Access to Research Initiative, which enables nearly 70 of the world's poorest countries to gain free access to biomedical literature through the internet.

The science publishers, Blackwell, Elsevier, Harcourt Worldwide STM group, Wolters Kluwer International Health and Science, Springer-Verlag and John Wiley, were approached by the WHO and the *British Medical Journal* in 2001. Initially, more than 1500 journals were made available for free or at significantly reduced prices to universities, medical schools, and research and public institutions in developing countries. In 2002, 22 additional publishers joined, and more than 2000 journals are now available. Currently more than 70 publishers are participating in the program.

Gro Harlem Brundtland, the former director-general of the WHO, said that this initiative was "perhaps the biggest step ever taken towards reducing the health information gap between rich and poor countries".

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