Perspectives

How can we explain the American dominance in biomedical research and development?

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The USA occupies a dominant position in high technology R&D and in the commercialisation of academic findings leading to new, innovative electronic products or in the case of biomedical research, better drugs. Why is this the case? Is it possible to isolate the success factors of the American system? Equally important is the question, for Europe and the Rest of the World, of whether it would be possible, by comparing both systems, to design the 'perfect' research and commercialisation environment, or is a marriage of only the ideal aspects of both worlds mutually exclusive?

The author spent seven and a half years in Boston, four years working as a post-doctoral fellow at the Children's Hospital, which is part of the enormous Harvard Medical School complex and three and a half years analysing new biotechnology investment opportunities mainly around Boston and the East Coast in a venture capital firm. Before that, eight years were spent as a hands-on laboratory scientist in three different research fields at the University of Vienna Medical School and the Institute of Molecular Pathology also in Vienna. These experiences should perhaps allow the author therefore, to compare the two systems in biomedical research. The reader can decide whether the Viennese period is a representation of a pan-European scenario and also whether the Boston experience mimics the USA in general.

Some of the differences are certainly generic and therefore they can be applied to both biomedical research and to other high technology areas like information, communication, or hardware and software computer technology.

It is the author's belief that distinct overarching differences exist and therefore a 'naïve' distinction of USA versus EU is possible. Nevertheless, such analyses should be considered an artificial construct and interpreted as such. The necessary, but unavoidable oversimplifications should not discourage from more and certainly fruitful discussions.

LINEAR VERSUS CHAOTIC SYSTEMS

Part 1: Decision making

In this paper, Europe is categorised as a linear society and the USA as chaotic or non-linear, for the lack of a better single-word description. This categorisation is not at all intended to be judgmental. Linear could stand for more rational,

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conservative, more bureaucratic, critical, hierarchical, organised, predictive, worried, social, more passive or ordered. Chaotic is not necessarily only the opposite but may be more open-minded, flexible, free-spirited, 'just-do-it' mentality, organisationally flat, aggressive or pro-active. 'Analysis paralysis' seems to be an important consciously and subconsciously well-accepted decision-making mode in certain important European countries, whereas the glass in the USA is most of the time half-full and not half-empty. *Hakuna Matata*, a Swahili expression for 'there are no problems' and *Carpe Diem*, a famous quote from Horace meaning 'seize the day', are more reflective and representative of the USA than of Europe. If this linear/non-linear segmentation is agreed, why is it important for the innovative potential in science and technology?

Although the main messages concerning decision making in a linear versus non-linear environment are certainly applicable to other high-technology environments, the example given here is from biomedical research. The development of a drug represents an even more complex dilemma because the time frames often span a decade and even more. In other words, it is very costly and difficult or even impossible to test different strategies to obtain a better understanding of what works or does not work in finding the next blockbuster drug. A simple example to illustrate just one single pitfall during drug development, is to estimate the market size potential of drug candidates entering late pre-clinical development. A current blockbuster drug with sales of more than US$1bn from a multinational pharmaceutical company was nearly terminated several times during early development because the market size was forecast as not sufficient to warrant the significant expenses. Several years before, the development programme of a similar compound was stopped in a biotechnology company due to analogous considerations — 'because there are not enough patients'.[1] This company would have probably been the first to market a drug in this indication. At present, the pharmaceutical company still has a monopoly probably because many other companies did similar market size estimates.

The go/no-go decisions in drug development are clearly much more complex than estimating the market size potential, but even for cash- and resource-rich companies, perfect information is not possible and linear thinking patterns will lead to inefficient decisions. The linearity dilemma lies in the fact that a single parameter with many unknowns, leads to the termination of a certain programme. Using probabilities to semi-quantify the different parameters is also not really possible because we do not know the odds with any reasonable precision. Biomedical research is a highly fragmented endeavour and useful statistical calculations are very difficult to do in many circumstances. It is interesting to note in this case that Sugen was a US-based company and the headquarters of the multinational pharmaceutical company, which decided finally to develop the drug, is in Europe. This might be the exception to the rule.

In this particular example, the drug shows a tremendous benefit for patients and therefore pricing was negotiated quite aggressively leading to a substantial revenue stream in excess of US$1bn within a few years, despite a limited patient population. The history of several currently very successful drugs reveals a similar story. Some of these drugs were in-licensed, out-licensed, sold and re-bought several times from various small and big players in the pharmaceutical industry.[2] In other words, the potential commercial value of these drugs was up- and down-graded more than once. If it were possible to predict the revenue generating potential with some degree of certainty, this would not happen but in chaotic systems, such accuracy is not possible. The danger lies in believing that it is feasible and in making decisions accordingly. This is where linear thinking has its limitations because if the conclusion is that, eg the market size is too small, the project will not be pursued. Using a more non-linear decision mode, the project might be moved to a point where better information is available or other options open up or are considered, eg out-licensing with buy-back options. This sounds trivial for those involved in these decisions but such flexible thinking might not be practised as often as it should be. Sugen decided not to develop these compounds although they would have been ahead of the curve by several years. The key message here should be that perfect information with forecasting is not possible and because we are dealing with chaotic systems where small changes can make a dramatic difference in the outcome, the forecasting mistakes might not only be plus or minus 20 per cent, but five- or even ten-fold. Promising programmes or projects therefore should not be terminated because the forecast value of a single parameter might suggest so.

To use the example of market size assessment, it is very difficult or in many cases impossible to estimate efficacy in clinical trials based on pre-clinical animal experiments. Nevertheless, efficacy is one critical component of pricing negotiations because in most cases the more efficacious a drug is, the more benefit the patients and society as a whole will gain. It is also a critical component to differentiate one drug from another.

Part 2: From high-risk projects to groundbreaking innovations

Background noise or waste is a characteristic of chaotic systems. The USA consumes per head about twice as much as European countries and therefore generates also about twice as much waste.[3] This might be one reason why they are more able to tolerate background noise, wasted resources, failed efforts and non-perfect information. The consumption-inclined-attitude of the American people might also play a role. In 2003, the household saving rate as percentage of disposable income was below 2 per cent in the USA, but above 9 per cent in Europe.[4] The 'non-critical, easy-going attitude' as described above might also play a role in this behaviour. Nevertheless, how does feeling more comfortable with 'wasting resources' lead to higher productivity in R&D activities?

It is almost impossible to predict the future value of funding for biomedical science or for scientific activity in any field of interest, but this is exactly the job of funding committees or agencies. However, because of the already described differences between Europe and the USA (linearity versus non-linearity; tolerance towards 'failed efforts'; 'easy going' attitude, etc.), it is believed here that the probability for a high-risk project to receive funding in the USA is significantly higher compared with Europe. The non-criticism attitude mode also helps in this respect. It is not trivial to define or characterise high-risk projects, especially prospectively, but they try to advance our knowledge not by small steps, they are not incremental, but by a significant move forward. High-risk projects have a higher chance to develop into quantum leaps and groundbreaking, revolutionary or paradigm-shifting technologies.

Thomas Kuhn phrased the term 'paradigm shift' in his famous book: *The Structure of Scientific Revolutions*. These ideas and projects are unconventional, untested and visionary. In Europe, these projects would not survive the partially endemic bureaucratic paths to receive funding. In the USA, they would probably also not survive the normal funding paths but several alternative money resources exist (eg DARPA, NSF, NIST, HHMI and private donations). Some of them have supported such projects for decades. In addition, significant amounts of 'private' money in the form of donations flow regularly into US scientific laboratories and this money can be used for unconventional research more easily than the resources from a government-sponsored programme. A high-risk project is often not suitable for government-based funding because, first some scientific data are required for submission and secondly, a (positive) progress-report has to be shown, to increase the likelihood of extension. High-risk projects frequently tend not to deliver the necessary results.

It is important to note in this context that high-risk projects must be based on world-class science or very reasonable and logical hypotheses and basic scientific concepts. They should not incrementally advance a certain sub-domain of a certain sub-sub-field but open entirely new scientific directions. Therefore, respected world-class scientists must play an important role in the decision-making process to fund such programmes. How such a decision-making process should be organised in order to fund the most innovative project is far from trivial.

The author believes that this tendency to support 'unusual' research activities is probably not planned but is a reflection of the American society — aggressiveness and daring might go hand in hand. It is difficult to speculate whether the Manhattan Project or the Kennedy Initiative 'to bring somebody to the moon' played a role in the development of this mindset over the last decades. In both cases, brute force in the form of money and world-class science were used to accomplish these difficult goals. Several similar programmes to find the cure for cancer have failed so far, but the mindset is still present that money and scientists can find a solution to specific problems. Investing large sums of money in a wrong paradigm will not lead to satisfactory results and it is speculated here that this is the reason for the almost overall lack of progress in cancer research.[5] Whatever the true reasons are, American laboratories take much more risk when they choose scientific projects and this attitude seems to pay-off handsomely in the long run.

If one believes the main message of Clayton Christensen's bestseller *The Innovator's Dilemma* that paradigm shifting technologies create significantly more value and earn much more money, one might have another important piece of the puzzle, why the USA is in general more innovative. Christensen shows that investing in paradigm shifts has been significantly more profitable than financing sustainable technologies. The probability of success is increased 6-fold from 6 per cent to 37 per cent and the total revenue stream 20-fold from US$3.2bn to US$62bn. Nevertheless, these numbers have been derived from analysis of the disk drive industry and extrapolation to other high technology sectors may not be justified.

The success formula might be the following: Americans are more aggressive, more tolerant of failure because they are used to waste and chaotic systems and are more willing to fund unconventional projects, which lead to higher value creation in the long term. Many of these projects do not go anywhere but some of them do greatly advance certain scientific areas significantly. Nevertheless, almost nothing moves without fuel and one essential ingredient for research is much more 'abundant' in the USA than in Europe.

MONEY AVAILABILITY AND DISTRIBUTION

Arguably, this is the single most important factor explaining the dominant role of the USA in innovative research. The total R&D expenditure in the EU was 1.99 per cent of GDP in 2002, whereas in Japan it was 2.98 per cent (2000) and in the USA 2.80 per cent.[6] In 2000, the gap between US and EU investment in R&D reached €124bn.[7] Assuming a conservative 10 per cent allocation to biomedical research, €12.4bn less was invested in Europe compared with the USA in 2000. The average cost of a drug developed by the pharmaceutical industry is estimated to be around US$800m.[8] In other words, about 15 new chemical entities could have been developed with this money. This number would even increase if one considers the cost of developing a drug by biotechnology companies. In 2002, the FDA approved 17 new molecular entities. Closing, or at least narrowing this financial gap, and not only in biomedical research, would make a tremendous difference for Europe.

The Howard Hughes Medical Institute[9] also plays an important role in the basic biomedical research-funding environment in the USA and has no equivalent in Europe. For 2004, the endowment was US$12.8bn. Members need to be appointed by other scientists or universities and therefore a significant selection pressure is at work supporting the top scientists with more resources. This might be the second most important factor explaining the difference between Europe and the USA. Scientific laboratories with 'Howard Hughes' status are highly regarded in the scientific community. It is also not uncommon in the USA for private individuals to donate tens of millions of dollars to build a specific research institute, or to support a Star-Scientist. Private individuals also often fund the endowments of professorships at prestigious universities.

Recently, venture capitalists lured academic scientists away from universities and funded their research very heavily through the creation of many new biotechnology companies. Over the last decade more than US$25bn went into private biotechnology companies and the majority of it into the USA. Table 1 shows the amount invested in private biotechnology companies between 1988 and 2003. The average ratio of investments into private biotechnology companies between the USA and Europe is approximately 5:1.

Table 1: Investment into private biotechnology companies between 1988 and 2003

Year	EU ($)	US ($)	US/EU
1989	144	335	2.33
1990	95	306	3.22
1991	87	272	3.13
1992	62	466	7.52
1993	57	432	7.58
1994	73	510	6.99
1995	118	830	7.03
1996	182	1,472	8.09
1997	250	2,133	8.53
1998	347	1,534	4.42
1999	643	2,193	3.41
2000	1,018	4,203	4.13
2001	844	3,418	4.05
2002	1,105	2,858	2.59
Total	5,025	20,962	5.21

Source: EVCA & NVCA (European Venture Capital Association, National Venture Capital Association)

In addition to government money, funding from non-government foundations and private sources, money from biotechnology and pharmaceutical companies also flows at a significant rate into the leading research institutions. Several articles and one book have been published recently about the commercialisation of academic research and the potential dangers involved in this recent phenomenon.[10–13] It is less of a concern for basic research, but causes significant headaches when clinical investigators test a new drug on patients and at the same time receive support for their laboratories from the company attempting to receive marketing approval for the drug. Some laboratory heads support a good proportion of their activities with industry money.

The conversion rate of private biotechnology companies into public entities through an initial public offering is significantly higher in the USA than in Europe. It is also much easier to have a substantial secondary offering further nurturing these companies with tens of millions of dollars, the majority without revenues. It has been calculated that on a per-company-basis, at least five times more money has been available in the USA compared with Europe during the last decade (Techno Venture Management, Boston office). In other words, using the example of drug development, if it is a pure probability game combined with some luck, US biotechnology companies have significantly higher odds compared with Europe to develop successful drugs. In addition, it should not be forgotten that drug discovery and development is not a linear process, ie five times more money does not mean five times more drugs.

Nevertheless, it is not only the total amount of money allocated to innovative research that is significantly higher in the USA, but probably equally or even more important is that the distribution is skewed. A few places receive a major portion of the money. Harvard, Stanford, MIT, Rockefeller and other prestigious institutions take an un-proportionate share of the money. As already mentioned, the endowment of Harvard University is above US$19bn. Assuming a conservative 4 per cent interest gain which is available to fund programmes at the University, more than US$700m would be available per year. Harvard University also leads the ranking in fund-raising. In 2003, it collected US$555m. The budget is certainly higher than the combined US$1,255m because other sources such as tuition fees need to be added. These are dimensions no European University can even come close to. And Harvard is not alone. In 2003, ten other US Universities were able to collect more than US$300m and 15 Universities had an endowment greater than US$3bn (data from the Council for Aid to Education, a subsidiary of RAND).[14] If Europe wants to compete successfully with such institutions, it needs to have some bold ideas and more important extreme political will to execute these visions.

It is not surprising that the Boston area is developing into the 'biomedical research centre of the world', housing MIT, Harvard University and Harvard Medical School. These academic institutions are fostering the creation of many biotechnology companies around Boston and combined, they feed each other and form an amorphous organism where communication flows almost effortless between the different entities. The very successful MD/PhD programme between MIT and Harvard Medical School is an example of such an exchange. A student at MIT can take classes at Harvard Medical School, Harvard Business School or Harvard University and vice versa. Economic clusters also allow easy movement of employees from one potentially failing company to another promising one. In some European countries, similar clusters not only of academic institutions but also of biotechnology companies have formed over recent years. Oxford and Cambridge in the UK, Munich in Germany or Basel-Zurich in Switzerland are examples. The biotechnology clusters in Boston, San Francisco or San Diego are important in explaining the US success story. Such structures might be even more important in Europe because employee mobility is less developed compared with the USA.

Assuming that one major innovative drive comes from these prestigious universities and the evidence strongly supports this hypothesis, what makes them so different? What is their magic recipe?

SELECTION CAUSES BRAIN BATTLES AND BRAIN DRAINS

To talk about student selection in some European countries is a political nightmare,[15] but it is believed here that it might be the 'Mother' of the American success story, especially in high-technology areas. Nevertheless, it does not seem to be sufficient on its own. France, Great Britain, and Japan have student selection systems in place but still cannot compete with the USA in these areas, although it is quite difficult to compare different systems because many other factors clearly play an important role.

In the USA, the SAT score is an important ingredient with which to obtain acceptance to Ivy-League schools and other prestigious institutions. The SAT system has been under heavy criticism for decades in the USA. Nevertheless, it leads to an accumulation of 'certain' students at 'certain' places. It is very difficult to find a reasonable 'selection factor' but, eg Harvard University selects about 2,000 students per year for College Undergraduate Admission. The theoretical selection factor at Harvard would be around 6,000 if everybody wanted to go there. In the USA, the enrolment number of undergraduates in 1999 was 12 million. In many European countries, the selection factor is zero. Imagine the quality of a sports team chosen from last year's high school students from a particular region of a European country compared with a team selected from the best 0.1 per cent of students in Europe assuming only a selection of 1 in 1,000. The concept of selection is already quite pervasive in the top European soccer clubs for example, but is so far relatively restricted to sport. The latest Programme for International Student Assessment (PISA) results[16] might cause a shift to more open discussions on this topic in some European countries.

In the USA, law, medical and business schools also use additional tests for admission to graduate programmes. Because starting salaries after graduation are significantly determined by the schools reputation, one can imagine how competitive it is to get into some schools. In Europe the COIMBRA Group[17] initiative tries to increase the quality of PhD level education at top European universities. This is certainly a very worthwhile activity, but should (must) be combined with student selection to produce even better results. It is interesting to follow the discussions in Europe on the PISA results[18] or the discussions about the quality of education. In almost all cases, the teachers are blamed for the unsatisfying results and rarely the students. This assumption needs to be questioned. If true, one way to mitigate this problem is a selection in addition to charging tuition fees. The motivation to have good grades might be positively influenced under these circumstances.

Another advantage of the American selection system is that strong bonds develop with the school and the US$19bn dollar endowment of Harvard University is a sign of this loyalty. Alumni reunions are held frequently and the attendance rate is high. In addition, alumni help each other with finding jobs or starting companies. They feel connected and this can make a tremendous difference. If two equally qualified individuals apply for a job and the decision maker is from, eg an Ivy-League school and one applicant is from the same school and the other one from a less well-known school, it is going to be an unfair game. These alumni networks are very powerful and certainly non-linear.

The energy level mixed with a very decent amount of competitiveness within the Harvard/MIT system is quite intriguing. It might be a self-fulfilling prophecy when foreigners come to these places because they might expect something unique and different but the author experienced a similar environment in Europe. It is more a question of selecting certain individuals than of geography. The brain-battles or ego-wars experienced on a daily basis are fascinating and enormously stimulating but not without a downside, as briefly eluded at the beginning of this paper. Individuals are very competitive and very motivated. In addition, at the prestigious universities, selection does not take place only at the student, but also at the professor level. Many professors are often recruited to these institutions only when they are well established in the scientific community and recognised worldwide. Who would not follow an offer receiving an excellent academic salary, very good financial support for research activities and in addition highly motivated students? This combination of double selection should lead to more ideas and innovative potential. The best professors filter and select the best ideas from very motivated and clever students, in addition to being able to pursue their own ideas with these students. This is an ideal win-win situation for both professors and students. Although the methodology is not without criticism, the worldwide ranking of Universities by the Institute of Higher Education, Shanghai Jiao Tong University, might reflect this situation. Among the top 20 universities in the world only three are not from the USA.[19]

The American University education system does also allow students to work practically and experimentally very early on in a specific topic or problem. It is not uncommon at MIT to see a 24-year-old graduate student starting a company with his or her professor after 2 years of basic science research, eg the Google founders were in this age category and were still students at Stanford. In many countries in Europe it takes a long time to finish the theoretical requirements even before extended time periods are spent in laboratories working on a specific topic. The upside of the 'European-style' system is that the depth of knowledge in certain domains is significantly higher. The downside is that it takes a long time to obtain this depth. The value of reaching this depth should be open for discussion. In the USA, students are 'used' much sooner by professors and obviously they gain a lot from this 'exploitation'. This system only works if the ratio of students to professors is reasonable. This ratio is certainly lower at prestigious American Universities compared with institutions in Europe. This might be another contributing factor to the imbalance.

To compare the US and European systems, it appears that the European system is more hierarchical and the professors 'use' the students to advance his or her career by telling him or her what to do; whereas in the USA, the motive of the professor is probably the same, but the student has certainly more freedom to choose a topic. The increased freedom combined with the lower age when such a choice is necessary, might also lead to more unconventional, unusual or daring projects, potentially leading to concepts with higher innovative potential. Taking risks at age of 22 is easier than at the age 28, especially if a 'family life' has been started already. The degree of 'radical thinking' is probably also higher at an earlier age. These distinct differences might be again a reflection of the intrinsic nature of the two societies and it might be difficult to simply copy the peculiarities of the American system without changes in society *per se*.

It must be also clearly stressed that a lot of the 'brain battles' at US universities are actually 'fought' by non-Americans. Europeans represent a significant percentage of all post-doctoral fellows in US biomedical research laboratories and biotechnology companies. The number of European, including former east bloc countries, Indian, Korean and Chinese computer and electrical engineers is also very substantial. In physical sciences, the rate is even higher. In 2003, a European Commission-initiated survey estimated that 400,000 EU-born scientific researchers are working in the USA and only 25 per cent have plans to return home.[20] This brain drain is very significant although especially after the dot-com bubble implosion and 9/11 a reverse brain drain or at least a decrease in the rate seems apparent. The changed political landscape in the USA, the resulting more stringent visa procedures, and the extension of the European Union to the East represent a unique opportunity for Europe to narrow the gap.

If one combines the aggressiveness of the American society, its ability to tolerate failure and waste, with unconventional thinking patterns leading to the design of high-risk projects; fuels this explosive mixture with significant amounts of money; selects the best professors and students and gives them early responsibility and freedom and allows and nurtures a positive brain-drain, the result might be the recent very successful innovative capacity of the USA. Last, but not least they all speak the same language.

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