Fundación Innovación Bankinter

19 ENGLISH VERSION

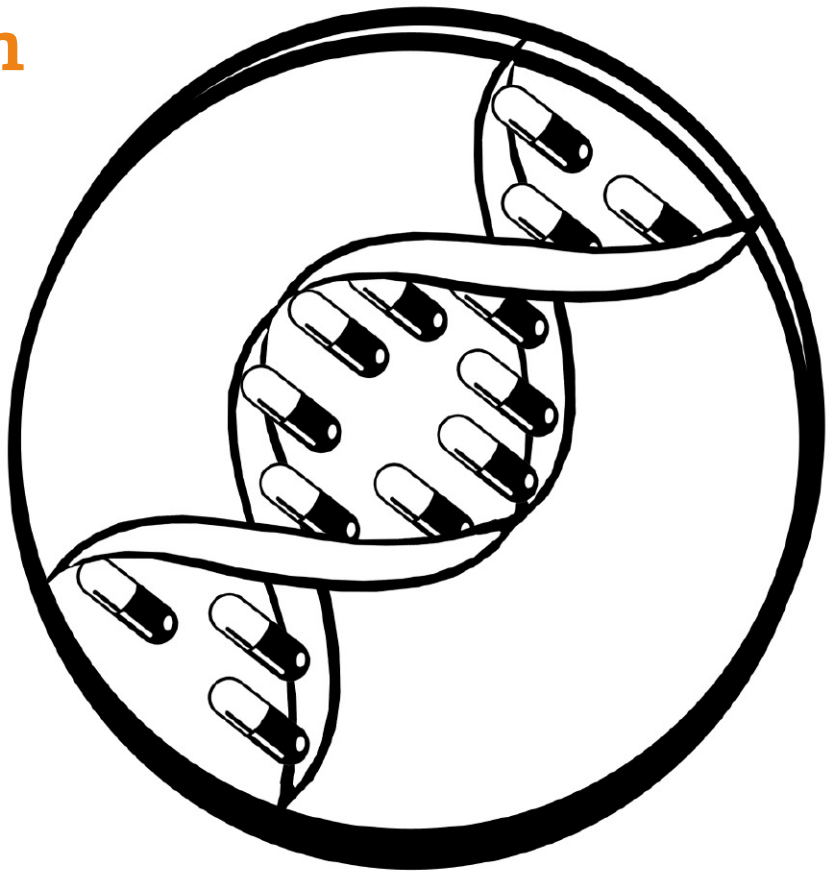
Disruptive Technologies
The Innovation Roadmap

Resource Allocation and Innovation
Public and private sectors, needs of patients

Academia-Industry Alliances
An Open Innovation Model

17 Proposals
To Promote Innovation in Drug Development

A Road Map for Increased Innovation in Pharma



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Many thanks,
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The Bankinter Foundation of Innovation

In a constantly evolving world, anticipating change and potential impacts in the medium to long term is the key to success. It is the way to identify and make use of future opportunities.
Bankinter created the Foundation of Innovation in 2003 with a clear objective: to have an impact on the present with an eye towards the future and to support the creation of new business opportunities based on cutting-edge technologies, ultimately to boost innovation among Spanish companies.

"Creating Sustainable Wealth through Innovation and Entrepreneurship"

The main mission of the Foundation is to boost and consolidate innovation among Spanish companies by strengthening its commitment to creating long-term value for all stake-holders—especially entrepreneurs and the game-changing players of our economy.
To this end, the Foundation looks for networks of knowledge to substantially promote innovation by anticipating new trends, while rigorously measuring results.
The Bankinter Foundation of Innovation builds its entire strategy upon constant innovation. During its short lifespan it has developed three projects with the ambition of promoting innovation tangibly and measurably with three horizons and three target audiences:

1. Big innovation trends in the medium term through The **Future Trends Forum**,
2. Effective support for innovative projects through the **Entrepreneurs** program.
3. Influence on future managers through the **Akademia** program in collaboration with academia.

Future Trends Forum

Future Trends Forum (Think Tank)

The Future Trends Forum (FTF) is the longest-standing and most consolidated project of the Foundation.

It is the only multi-disciplinary, cross-sectional, international think tank focused on innovation. It is made up of an exclusive group of 350 experts and opinion leaders from five continents. Their main objective is to anticipate the immediate future by detecting social, economic, scientific and technological trends, and analyzing their possible scenarios and impacts in current business models. To this end, they meet twice a year to discuss trends.

By drawing international talent to Spain, the FTF makes an effort to get ahead of the curve, fill in a void, and contribute to a more advanced and competitive society.

Our constant commitment has earned us the recognition of **"The Think Tanks and Civil Society Program"** of the University of Pennsylvania, which in 2012 ranked us as number **25 in the Science and Technology think tank worldwide ranking**. We are the **only Spanish** think tank to be listed in the **"Global Go-To Think Tank Index."**

This ranking analyzes over 6,500 think tanks worldwide. It is put together based on a survey of more than 1,500 scholars, politicians, journalists, and worldwide experts, and structured per region and activity. It is worth noting that we are the only Spanish think tank on the list, one of seven European institutions, and the only one fully dedicated to innovation trends.

In the XIX Future Trends Forum, **"The Future of Drug Discovery,"** our experts analyzed the future of the drug development process from inception to marketing, specifically the role of innovation, and new technologies in the pharmaceutical industry.

The XIX Future Trends Forum brought together representatives of the pharma and biotech industries, startups, basic research, business management, investment funds, open innovation, public administrations, patients, and new technologies.

The goals are to analyze what fields or tools will ignite a revolution in drug development, what business models will solve structural problems, what the priorities in public and private research are, what the solutions to align knowledge and innovation are so that the chance of transforming them into products increases, and what alternative access to funding there is in a complex environment.

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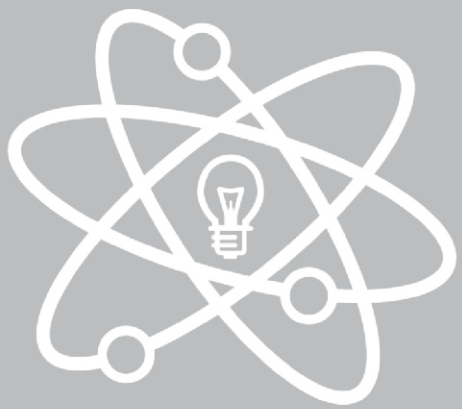
Innovation and Connectivity



The Perfect Storm

José María Fernández Souza
President of Zeltia Group. President of the Bankinter Foundation of Innovation

Over the next fifteen to twenty years we may experience a drastic reduction in the number of innovative drugs approved. The reason would be something we might call "the perfect storm," on the edge of which we are standing right now. This storm is brewing with three components. One: regulators and healthcare authorities that are taking increasingly more time to approve new drugs, thus making the process more expensive for companies. Two: governments that are reluctant to pay the bill for new marketed compounds due to the already heavy burden of health care on public budgets. Part of the reason behind this is that drug discoveries were, and are, precisely the key to greater longevity, which of course increases public healthcare spending. And the third reason for the perfect storm are pharmaceutical companies who are becoming increasingly conservative, since developing innovative medicine requires increasingly more time and investment in a risky environment.

Over the next fifteen to twenty years we may experience a drastic reduction in the number of innovative drugs approved.

I would like to analyze in some detail each of these sources of problems. What is the situation from a regulatory standpoint? Twenty years ago, marketing a new drug took eleven to thirteen years (depending on the therapeutic area) and cost an average of $300 million. Today, **it takes twelve to sixteen years, and its development requires an investment of up to $1 billion in quite a few cases**. Significant delays are occurring in various stages of clinical trials. Fifteen to twenty years ago, the approval from stage I to stage II took approximately three months, and the same applies from stage II to stage III; whereas today, the average is one year, ranging from seven to fifteen months. This **reduces the lifespan of the patent**. The longer periods are due to the fact that regulators want to be certain. They act as if instead of approving from one stage to another they were considering the actual, final approval of the drug. The problem has already been raised at the European Medicines Agency, and a commitment to reconsider the situation in 2016 has been granted (particularly the stage approval procedures of ethics committees in clinical trials). In all honesty, we are facing a considerable problem: while other innovative industries succeed in marketing their products in shorter times, the times of the drug industry are becoming increasingly longer.

Develop innovative medicines requires increasingly more time and investment in a risky environment.

Governments face healthcare funding with caution. People today live longer thanks to drugs, which increases the cost of health care. Partly because of this, administrations take longer to set the price of drugs, and then refund the amount covered by the State. The delay in payments is a particularly acute problem in Southern Europe. In other industries, inflation is reflected in the price of products. In the drug industry, however, the initial price is lowering. On the other hand, when the FDA approves a new substance in the United States, it can basically be marketed immediately. In Europe, once the European Commission approves a drug, the pharma company embarks on a country-by-country excursion to negotiate price and refund terms with the public healthcare systems. This process lasts from two to four additional years to effectively market the product in the 27 member states: two to four more years to be subtracted from the patent lifespan.

Add public cuts in R+D to this horizon. For example, over the last decade, the American NIHs have suffered budget cuts of 20%, that is, $6 billion. **And governments are clearly interested in having generic drugs in the market as soon as possible, which proves detrimental to research in new drugs**. This phenomenon is forming a vicious cycle because if you add the pressure of the administration favoring generics to the **ever shorter period of time to recoup the investment in innovative drugs**, companies will of course try to recoup their investment by negotiating a higher price.

And what is the situation at the helm of big pharmaceutical companies? Their presidents and CEOs are held accountable to their shareholders every year, and they must show results. The easy and tempting solution is to cut R&D spending which is risky and will only bear fruit in ten to fifteen years time at least. According to the figures of the big industry, **developing a new drug requires $1 billion**, and given the risk and uncertainty linked to the investment it is understandable that decision-makers would rather spend $1 billion in acquiring a generics or cosmetic company, or any other type of investment. **R&D investment in the US pharma industry is estimated to decrease by 5.7% this year**. Decision-makers are becoming more risk-averse lately because the first line of management is increasingly fearful of mistakes—hence the ensuing impact in innovative research.

R&D investment in the US pharma industry is estimated to decrease by 5.7% this year

Risk-aversion is precisely the common denominator I see in this perfect storm. Regulators have it, since they want to be confident of each approval granted, and this accounts for the longer times. Big pharma companies have it, since their decision-makers risk their jobs with mistakes that may cost hundreds or thousands of millions of euros. It affects investors, who are skeptical about a return as they see approval periods extend. And governments have it, showing their lack of vision and coordination at times.

This is why the reflections of the Future Trends Forum are so important: If we want to have innovative drugs in fifteen or twenty years, we must propose efficient solutions now.

Innovation and Connectivity

Elvira Sanz
President of Pfizer Spain. President of *Farmaindustria*

If we analyze the recent evolution of the GDP and healthcare spending in the US and project it into the future, we will find that **by 2050, 90% of the GDP will be spent on health care, and by 2082, 99%**. This trend is obviously unsustainable, and the situation is quite similar in Europe, therefore we must reconsider our healthcare systems and accelerate the pace of change now.

Furthermore, an aging population will put more pressure on the situation. **By 2050, 40% of the population in Europe will be older than 60 years of age**. It is well known **that 80% of healthcare costs generated by a person throughout their life is when they reach 60 years of age and older**. These two factors combined lead to a predictably critical situation in the medium term.

The issue is **sustainability, and it** is an issue on both sides of the pond and beyond.

Growth in R&D investment is not compatible with the current decreased productivity

The pharmaceutical industry has traditionally shown an investment capacity sustained over time. However, **growth in R&D investment**—back in the day it was exponential—**is not compatible with the current decreased productivity**. The number of new drugs in the market has clearly been reduced. This is a global phenomenon that is common to different therapeutic and geographic areas.

R&D is changing: Biomarkers, experimental drugs, combinations of therapies and vaccines, new technologies, opportunities offered by e-health, etc. all make up a different reality. There is no doubt **the scenario has changed, but it will not provide sufficient innovative drugs as quickly as needed**. While the cost of developing drugs is rapidly increasing, the expectations of different players are changing: from doctors to patients and regulators, and those who pay for health care. We all want safer drugs with greater efficacy and affordability. Reaching this goal is nothing short of impossible if we continue to operate our R&D machinery as we have in the past.

The public healthcare agenda is another factor that is undoubtedly redefining the pharmaceutical industry. Healthcare issues, as well as political influence and economic interest converge in this agenda. Let us not forget

To reduce the risk we must make the right decisions regarding the development of new early-stage therapies

that in these times of uncertainty and global crisis, the venture capital cycle has changed completely.

Today we know more about diseases. The more we know, the more evident it is that needs are not being met. How do we react in these times of re-definition? How is the pharmaceutical industry adapting?

In this complex scenario, **the industry recognizes that it is essential to develop innovative drugs** in order to truly fulfill unmet needs, and that are afforded by governments and insurance companies.

We need to **reduce the risk linked to the development process, or we will not find investors willing to invest in our companies**. To this end, we must make the right decisions regarding the development of new early-stage therapies. Statistics reveal that **one in three drugs that makes it to stage III does not make it to the market; at this point, up to 60 or 70 percent of the cost of developing a drug has already been invested**. Therefore, there

is a lot of room for improvement in the decision-making process. A good decision is financially much better the sooner it is made.

Additionally, **reducing the development time** is vital. The time that elapses between the various trial stages is hindering all pharma companies, since close to **30% of a new drug's development time is wasted waiting for approval from one stage to the next**.

Pfizer has adopted four strategic requirements that are transforming our approach to R&D and I believe are shared by most big pharma companies:

1. **Detecting unmet needs of patients**
2. **Supporting precision medicine**
3. **Seeking scientific and business innovation**
4. **Promoting strategic outsourcing**

30% of a new drug's development time is wasted waiting for approval from one stage to the next.

Regarding the first point, a **streamlining process** is essential. Five years ago, Pfizer focused on 16 therapeutic areas, including over 170 programs. Today, we have sold or winded-down many of them, so we now have less than one hundred programs running. We now focus on 5 specific therapeutic areas that we believe have a greater chance of success from a scientific and business standpoint: neuroscience, cardiovascular diseases, vaccines, oncology, and inflammation and immunology. There are as many as 95 molecules in the various stages of development or registration. However, we must acknowledge **that the less we explore the pathology, the greater uncertainty there is throughout the discovery process**. Alzheimer research is a clear example of this. As echoed by mass media, we had to suspend the development of bapineuzumab a few months ago. This substance was developed with the hope of becoming the first modifier of the disease by acting on beta-amyloid plaques. Bapineuzumab had been under study for twelve years and was already at stage III. Cases like these are relatively common.

Precision medicine is a promising path to transforming knowledge about a disease into clinical results. We have several compounds in stage II, stage III, and even in the process of being registered, that fall within the category of precision medicine. For example, crizotinib was designed to target non-small cell lung cancer in patients suffering from ALK gene translocation who make up 5% of lung adenocarcinoma patients. To put these figures in perspective, suffice to consider that there are 150,000 cancer patients in Spain, out of which 20,000 suffer from lung cancer, and 450 of those suffer from this specific type. Before crizotinib, life expectancy for these patients was two months; today more than 80% of patients treated

with crizotinib are alive for two, three, four years.... It is a glimpse of the potential for **precision medicine**. The question is, who will fund it? **What is the price of a compound that benefits 450 patients in Spain, and 5,000 in the whole of Europe?** These questions, still unanswered, are raised by precision medicine.

The third pillar of our strategy is essential. We are certain that improved R&D productivity, to a certain extent, will come along with new technologies such as mixed anti-bodies, vector drugs, cell therapies, etc. This type of approach takes up a significant portion of our current efforts.

Finally, the fourth area of change we are promoting builds on outsourcing, on promoting **a notion of global innovation, and on seeking talent and knowledge beyond the borders of the company itself**, especially in the United States where we have detected R&D ecosystems made up of biotechnology companies, university research centers and startups. **Forging a solid relationship between Big Pharma and Academia**, where each is respectful of the other's role, **will allow investors to find our research appealing once again, and make its risks more acceptable**.

Improved R&D productivity, to a certain extent, will come along with new technologies such as mixed anti-bodies, vector drugs, cell therapies

Pfizer is very active in this regard. We work under the **Therapeutic Innovation Centers (TICs)**, and these groups are doing something different, something special. We do not intend to transform them; we merely assist them while maintaining their essence. We grant them access to our data bases, we assess them so as to maximize their patent rights, we assist them with publishing, we provide economic incentive, and more, but we do not acquire them since their strength resides in the way they operate, as well as their flexibility and their size. Today we have three clusters in the United States—in California, Boston and New York—under this arrangement, grouping a total of 90 centers.

In short, **R&D strategy is in need of a complete overhaul** and we are already working on it in my company. We are redefining and streamlining our areas of research, and we are outsourcing and becoming digital. We scout for talent and innovation, and we forge alliances. We believe words like "change" or "evolution" are no longer useful. **Today we need "revolution" or "disruption,"** and that is something the Future Trends Forum provides us.

We should not believe that we are unique since many innovative industries have reinvented themselves. I would like to wrap up with the example of the film industry. Years ago, movies opened with the logo of a big producer. Today they do so with a sequence: the big producer, a mid-sized producer associated to yet another one, and in collaboration with yet ano-

R&D strategy is in need of a complete overhaul. Today we need "revolution" or "disruption

ther one. We see many similarities with this evolution. Let me assure you, our next innovative drug will not have been developed by Pfizer only, but by Pfizer in association with another company, thanks to the discovery made by a yet another laboratory or scholar, etc, etc…

Without any doubt, **connectivity and synergies lay in the future.**

Chapter II: Disruptive Technologies: The Innovation Roadmap

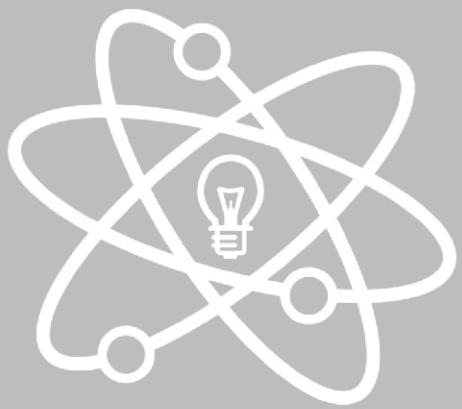
Biomarkers

Genetics, High-throughput Screening and Bio-informatics

Nanotechnology: When Medicine Talks to Cells

Cell Therapy: a "Nobel Technology" with Long-Term Potential

From Genetic Knowledge to Prevention



Andrew Hessel

Autodesk Distinguished Researcher Faculty, Singularity University

Reinventing Drug Development

At some point we have to face facts. Drug development is broken.

The present system isn't optimal for anyone – companies, consumers, doctors, regulators, or investors – yet making meaningful change to it has been elusive.

In 2009, Bernard Munoz of Lilly reviewed the outputs of the biopharmaceutical industry[1]. The results were startling. His numbers painted a dismal picture: for six decades, just a few dozen new molecular entities (NMEs) or biologics were made each year.

Charted as R&D dollars spent per new drug, the trend is *exponentially negative* productivity. This means that while the biopharma industry is a great user of technology, the business of drug development itself is not a technology. To the contrary, it's an unsustainable sinkhole, failing despite the talent and money and technology being used to prop it up. And it's not meeting the medical needs of most of the world's population.

So why continue to throw good money and effort at such a bad system? Why not take a bold step and accept drug development for what it is – obsolete – and start again from scratch?

It's not hard to imagine what a better drug development process might look like. It would put the needs of the consumer first, whether this was a large group of people or a single individual. It would produce new me-

[1] Munoz, B. 2009. Nature Reviews 8: 959

dicines quickly and inexpensively. Researchers and developers would be able to work together easily to make new drug designs or trials or to flag concerns. The process would be transparent to consumers and regulators. The outputs would be affordable. It would be profitable.

Building such a system is possible. In fact, it may even be happening spontaneously, fueled by changes in technology, business, and society. Some leading indicators include:

- **Synthetic Biology** – an emerging field that seeks to make genetic engineering standardized, fast, and reliable – and has already attracted billions in public and private investment
- **Social Medicine** – individuals, groups, and communities self-organizing to better manage or identify diseases, for example Patients Like Me and Rare Genomics Institute
- **DIYbio** – citizen scientists exploring biotechnology at home and in community laboratories
- **Quantified self** – a global community interested in tools, technologies, and processes for self-measurement and self-treatment
- **Consumer Genetics** – 23andME, Knome, Counsyl, uBiome, and the Personal Genome Project are each examples of groups bringing genetic analysis and screening directly to end-users
- **Online CROs** – need some DNA sequenced, a gene expression experiment performed, or a protein expressed? Go online to Science Exchange or Assay Depot with your ideas and your credit card
- **Crowd funding** – Research and development projects supported not by academic or industry grants but directly by interested individuals
- **Incentive Prizes** – the X Prize Foundation has $10M US challenges in medical grade DNA sequencing and a handheld "Tricorder" for rapid diagnostics

More than ever, smaller groups are empowered to compete with much larger organizations. This opens the door to alternative strategies R&D strategies.

For example, governments or health agencies could create open challenges for antibiotics or vaccines, medicines that have fallen out of favor with developers. The US Defense Advanced Research Project Agency (DARPA) and X Prize Foundation have both demonstrated that incentive prizes can punch through innovation barriers and leverage prize dollars. Similarly, Innocentive Inc., an innovation broker, also sees many solutions get posted for well-defined problems by their large community of "solvers". Both

approaches allow broad ingenuity to be tapped while keeping R&D costs and timelines constrained.

Another change driver could be personalized medicine. The present industry seeks to develop blockbuster medicines ($1B US annual sales) but has failed to produce economies of scale. Because it costs about the same to make a drug for one million people as one thousand people, drugs that have fewer eligible consumers cost proportionally more. This equation, however, may not apply for medicines made specifically for one person (n=1 or fully personalized medicines) because the normal development and approval processes, including phased clinical trials, simply don't apply.

With a fully personalized medicine, the consumer would be intrinsic to the development process. From the outset, they would be cognizant of the risks versus the benefits, and perhaps even funding the development. With only a single client, regulatory approvals, if sought at all, should be relatively easy to secure, and the liability for the developers would be the theoretical minimum. The drug maker's challenge would move away from finding the best drug for the myriad variables of a mass market product, to finding the best solution for one unique client.

As little as a decade ago, development of an individualized medicine would have been impossible to consider. But things have changed. Deep metabolic and genetic analysis can be done for individuals at reasonable cost, and customized treatment strategies are becoming more common. Large chemical libraries are available for purchase. Automation and standardized assays permit high-throughput screening.

Synthetic biology, computer-aided genetic engineering, could also prove transformative. Synbio has already been applied to the development of conventional medicines such as the antimalarial drug artemisinin and synthetic antibodies, and also for more exotic therapeutics, such as "nanorobots" based on DNA origami. Meanwhile, the core technology of DNA synthesis continues to improve rapidly, enabling more sophisticated designs.

Synthetic viruses are particularly interesting. Viruses are versatile agents that have been used in hundred of experimental clinic studies as gene therapies, antibiotics, and as anti-cancer agents. They have compact genomes and minimal manufacturing requirements. This makes them an attractive platform for personal-scale drug development.

Academic and commercial "biofabs" have already emerged for engineering bacterial species. Dedicated virus fabs may not be far behind. Combined with software tools better able to tap the expertise of virologists around the globe, fabs could make custom-engineered viral therapies become technologically and economically feasible in just a few years.
Should drug developers be worried? Absolutely. The shortcomings of today's industry is the perfect breeding ground for disruptive change. The convergence of accelerating technology, online information, and community-based initiatives in biology and medicine bring foundational change to the drug development process. The tension hangs in the air today. All it may take is a spark to inspire breakthrough innovation and change – perhaps the emergence of a new pandemic, perhaps a single individual with a compelling medical need.

Change will happen. If Munoz is correct, it must happen. Indeed, grassroots efforts are already happening in rare diseases, where individuals with undiagnosed genetic disorders have sparked crowd-sourced and crowd-funded efforts launched to help them[2]. It's only a small step from this point to open source drug development. As "fabs" become more powerful, personal scale contract development of chemicals and biologics could appear – a paradigm shift built one drug, one person at a time

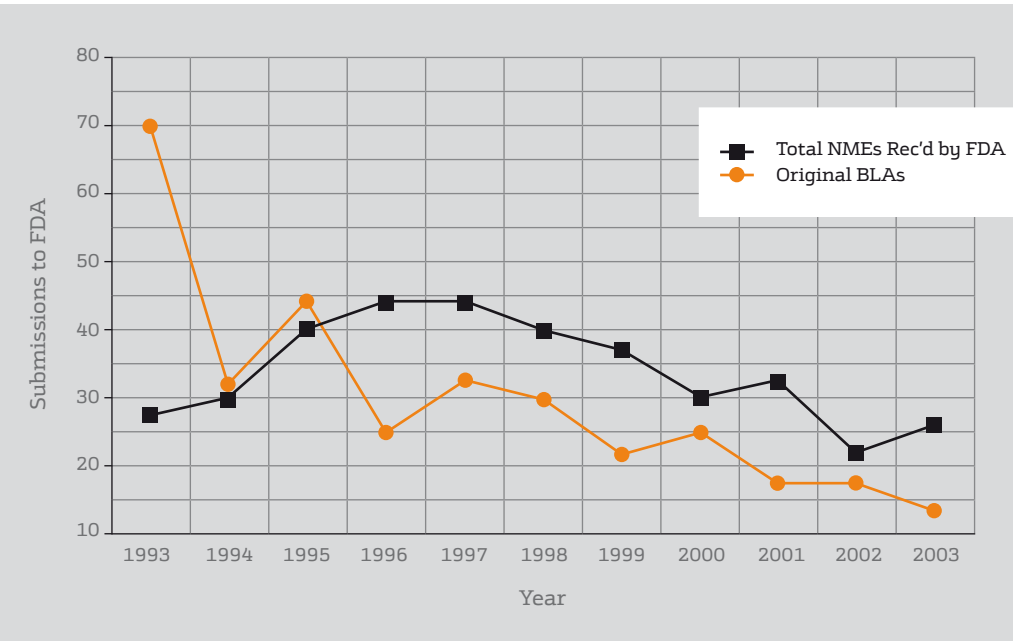
[2] http://raregenomics.org/donors.php

The pharmaceutical and biotechnological industries top the worldwide ranking of research investment

According to the *Table of Indicators on Industrial Investment in R&D in the European Union* **2011, the pharmaceutical and biotechnological industries top the worldwide ranking of research investment. They account for 17.7% of global research in R&D**, followed by technology and information system equipment (16.8%), and cars and components (15.8%). The car industry leads investment in Europe, followed by the pharma industry, according to the EU classification.

This very table reveals that there are **four pharmaceutical companies in the top ten R&D investors worldwide: Novartis**, which allocated €7.1 billion to this end in 2011; **Pfizer and Roche**, with €6.8 and €6.7 billion respectively, and **Merck**, with €6 billion.

A sustained effort does not always translate into results, since **only one in ten thousand molecules researched becomes a viable product**. From 1993 to 2003, funds allocated for research by the National Institutes of Health (NIHs) of the United States and the pharmaceutical industry grew by 250%. In that same period, the number of new molecular entities and biodrugs presented to the FDA for approval experienced a clear decrease.



Source: FDA, Critical Path Initiative, Challenges and Opportunities Report, 2004

In the meantime, the level of uncertainty in the industry–a determining factor for attracting investors—has increased because **the cost of developing drugs is growing significantly**, even when comparing short periods of time. From 1995 to 2002 the investment required to develop drugs—from the discovery of the substance to its launch into the market—**increased by 55%**, mainly **due to the increase in the costs of clinical trials**.

If you expand the time span, from 1950 to 2007, the cost of developing each new molecular entity experienced a compound annual growth rate of 13%. **The investment needed to develop a new drug today is over €800 million. However, only one in five becomes a blockbuster**[1].

Hence, the pharmaceutical industry is facing the challenge of finding uncharted fishing grounds of innovation to provide more effective solutions for the needs of patients, and guarantee a return on a long-term investment.

For the attendants, the six areas that will revolutionize diagnosis and treatment are synthetic biology, biomarkers, genetic information, high-throughput screening and bioinformatics, cell therapy, and nanotechnology.

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[1] Nature Reviews Drug Discovery, December 2009, p 959-968

Biomarkers: Putting Last Names on the Disease

According to the US NIH consensus, a biomarker is "a characteristic that is [objectively] measured and evaluated as an indicator of normal biologic processes, pathological processes or pharmacological responses to a therapeutic intervention[2]."

For 25% to 40% of those who receive the drug, the substance is completely ineffective

The efficacy of the main drugs for severe diseases (such as cancer, diabetes or autoimmune diseases) **is 25% to 60%**. This means that for 25% to 40% of those who receive the drug, the substance is completely ineffective, even though it may have side effects. In today's science, drugs are used not knowing from the start whether they will work for a specific patient, or whether they will cause more harm than good due to the side effects.

LIMITED EFFICACY	
Response rate to conventional treatments in a selection of therapeutic areas	
Areas	**Efficacy %**
Alzheimer	30
Painkillers	80
Asthma	60
Arrhythmia	60
Depression	62
Diabetes	57
HCV	47
Incontinence	40
Acute migraine	52
Migraine (prophylaxis)	50
Oncology	25
Osteoporosis	48
Rheumatoid Arthritis	50
Schizophrenia	60

Source: Spear at al. Trends in Molecular Medicine, Vol. 7, No. 5, 2011

[2] Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther 2001; 69: 8995.

Russell Howard, CEO of **Oakbio** —a biotechnology firm pioneering the development of microorganisms for capturing CO2—and cofounder of Maxygen—a biopharmaceutical company focused on developing a treatment for chemotherapy-induced neutropenia—presented at the XIX FTF on how **biomarkers are already changing pharmaceutical research**, and the paradigm shift they may bring in the medium term.

According to Howard, **biomarkers will radically modify the way health care is provided** since they will allow:

- carrying out a test indicating an individual's likelihood of suffering some disease;
- [predicting] what yet not present disease is the individual very likely to suffer in the short term;
- in case there is a present pathology, biomarkers will indicate what the disease is specifically, at what stage it is, and what the probabilities are of various evolutions;
- furthermore, **biomarkers will indicate what drug or combination thereof will work for a particular patient, and** what drug has the highest benefit versus side effects ratio.

In addition, **biomarkers will be added to the first stages of drug development**. "We will probably have biomarkers that are signals in *in vitro* or animal trials telling us that a certain compound will have poor efficacy in humans. And this is quite significant for R&D investment because the earlier you can discard a substance, the better," he says.

Biomarkers will indicate what drug or combination thereof will work for a particular patient

This applies to the various stages of the disease, starting with the preventive stage. There is a constant search for biomarkers that alert us to the predisposition of developing diseases such as type II diabetes or neurodegenerative diseases such as Alzheimer's. "With more detailed sequencing of the human genome, it is not crazy to imagine that in two decades time, the four to five most likely pathologies to be present in a person may be predicted—and in no few cases, acted upon by adopting a certain lifestyle—and if the disease becomes present, what drug will be most appropriate," says Howard.

Biomarkers enable an accurate identification of the type of pathology a patient suffers, which is absolutely essential in cancer. Furthermore, in this area there is a close association between the discovery of the diagnostic biomarker and the initiation of therapeutic strategies. It is as if we used to know the given name of the disease and now we've discovered the last name.

One example is triple negative breast cancer which is treatment-refractory to available treatments with the highest efficacy, hence the high relapse rate. A recent study by Vanderbilt University (Tennessee, United States) has identified that the protein TGF-β is overexposed in triple negative tumor cells after chemotherapy, meaning, this is a new specific biomarker for treatment resistance. Animal models used by researchers show this protein is the reason why healthy cells become cancerous and the disease reappears after a while. Moreover, blocking the protein prevents tumor recurrence, thus suggesting a potential therapeutic pathway against this particularly aggressive modality of breast cancer[3].

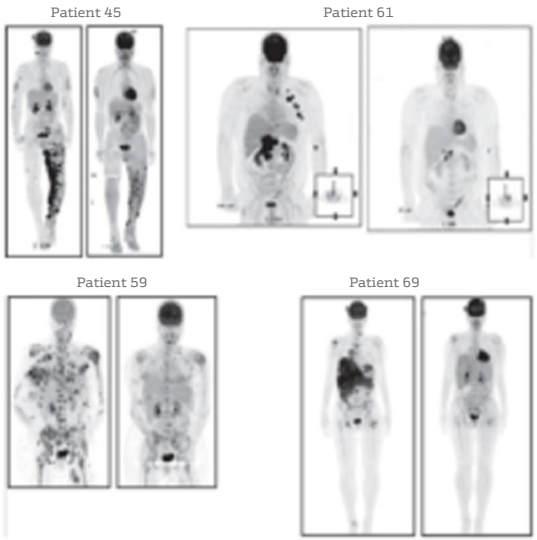
Vemunarefib is a therapeutic success story based on biomarkers. This compound acts against metastatic melanoma, the most aggressive type of skin cancer, for which there was no treatment whatsoever until recently. The key was finding a biomarker: the BRAF gene codes the homonymous protein which is overexposed in a little more than 50% of metastatic melanomas. Based on this, Roche developed vemunarefib which acts precisely by inhibiting this protein, which in turn stops the progression of cancer in 80% of patients. The first results of the clinical trial in humans[4] were published in August 2010, the first significant progress made against melanoma in twenty years. The FDA approved it one year later followed by the European Commission in February 2012[5]. There are many compounds that follow this path (for example, the FDA approved vismodegib in 2012 to treat metastatic basal cell carcinoma, another type of skin cancer), which may radically change the approach to cancer.

There are many compounds that may radically change the approach to cancer.

[3] J Clin Invest. doi:10.1172/JCI65416.

[4] N Engl J Med 2010; 363:809-819

[5] Official Journal of the European Union C 94 de 30.3.2012, p. 2



Source: Nature 467, 596–599 (30 September 2010)

Images show the extent of the melanoma before (left) and after (right) two weeks of treatment with PLX4032, a molecule resulting from biomarker research that developed into the drug vemunarefib.

Positron Emission Tomography (PET) can visualize a substance rich in sugar and that tumor cells avidly consume.

Biomarkers are also used in imaging diagnosis. Positron Emission Tomography (PET) can visualize a substance—an amino acid analogue—rich in sugar and that tumor cells avidly consume. When administered to the patient, the PET shows an accurate image of the size of the tumor, indicating, for example, if it has shrank with the first cycle of chemotherapy, or if a more aggressive treatment is necessary. This application is very important in brain tumors such as glioma[6], with an average life expectancy of one year after diagnosis.

Biomarkers entail challenges for the stakeholders involved in drug development, from patients to governments, to clinical researchers and the

[6] Scientific Paper 250: Johannes Schwarzenberg, Timothy Cloughesy, Johannes Czernin, Benjamin Ellingson, Whitney Pope, Daniel Silverman, Cheri Geist, Michael Phelps, Wei Chen; David Geffen School of Medicine at UCLA, Los Angeles, CA; "Metabolic tumor volume by 18F-FDOPA PET is predictive of treatment response in patients with recurrent high-grade gliomas on anti-angiogenic therapy as early as 2 weeks after therapy initiation," SNM's 59th Annual Meeting, June 9, 2012, Miami Beach, Fla.

The challenge is to extract clinically significant data from the millions of data, figure out how to transfer information to biology, and biology to Medicine."

big pharmaceutical companies, as highlighted by Russel Howard. The first challenge, of course, is that "they must be subject to drug-analogue procedures to prove that a particular biomarker has predictive value, in clinical terms." Furthermore, "a reasonable path to guarantee a return on investment is yet undefined." On the other hand, researchers and administrative authorities have an unprecedentedly large universe of data before them: "We are not short of technology; our problem lies in the complexity of the information provided by technology. The challenge is to extract clinically significant data from the millions of data, that is, figure out how to transfer information to biology, and biology to Medicine."

Genetics, High-Throughput Screening and Bioinformatics

The answer lies in the genome. Genetic variations influence the likelihood of suffering a disease, but environmental factors—food, physical exercise, use (or avoidance) of toxic substances such as tobacco or alcohol—have a decisive influence on the phenotype, that is, on whether the genetic characteristics become active or not. In this regard, **"knowing our predispositions enables us to adopt preventive measures,"** according to **Esther Dyson**, president of **EDventure Holdings**, and attendant to the XIX Future Trends Forum.

Not everything is negative predispositions in the genome. A rare genetic variation stops the human immunodeficiency virus (HIV) from infecting white blood cells, so carriers of this variation are protected.

A rare genetic variation stops the human immunodeficiency virus (HIV) from infecting white blood cells

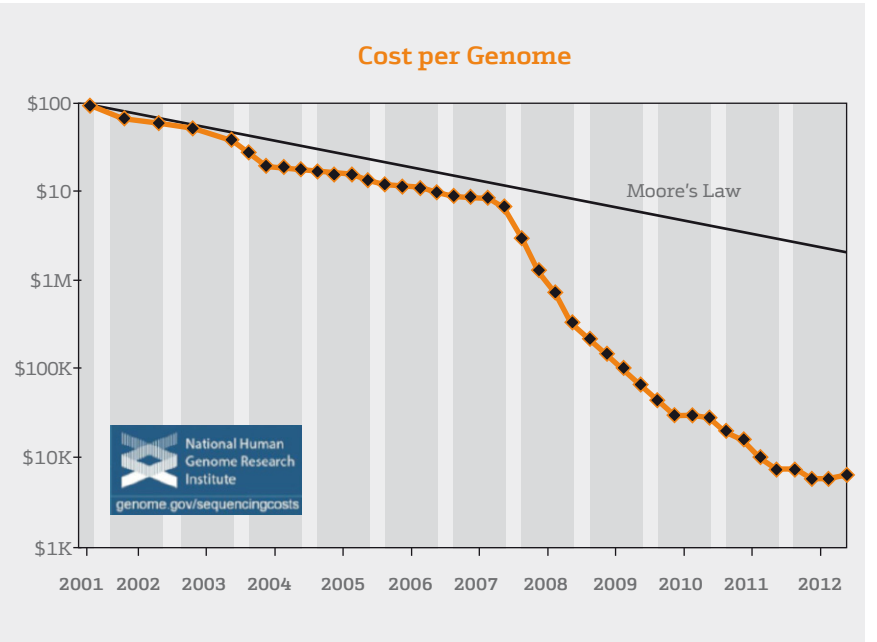
The more the genome is studied, the more data it provides. In 1999, it was discovered that the MECP2 gene was directly involved with Rett syndrome, a postnatal genetic disease that mainly affects girls. Today it is known that not only the protein is important, but also the location where the mutation is produced which affects the prognosis of the disease; so if it is located in amino acid 273, then the life expectancy is higher than in amino acid 270[7].

A similar phenomenon occurs with cancer. Tumors today are classified based on their location or morphology, but in the near future, they will be classified based on the mutations to which they respond, since their genetic composition determines both the likely evolution—and therefore the prognosis—and the reaction to the treatment. In other words, it will let us know which drugs will or won't be effective. This is already taking place with breast cancer.

One of the reasons this is one of the most promising areas is **that the processing capacity of the technology has experienced exponential progress, while costs have progressed in inverse proportion**, according to **James Coffin**, vice-president and general director of Dell Healthcare Life

[7] Cell 152(5) pp. 984 - 996, 28 February 2013

Sciences, who presented at the XIX FTF Forum on the potential of high-throughput screening.



Today, Dell Healthcare Life Sciences has sequenced a child's genome in four and a half days for slightly under $10,000

Human genome sequencing took ten years and $3 billion. Today, Dell Healthcare Life Sciences has sequenced a child's genome in four and a half days for slightly under $10,000, according to Coffin. Based on the information obtained, the genetic profile of the tumor is built—in a project with the Translational Genomics Research Institute—narrowing the treatment of child neuroblastoma to four or five good drug candidates. This strategy not only reduces the toxicity for the child, it also increases the likelihood of tumor remission by 30% to 40%, whereas the survival rate with traditional methods is at around 3%.

The first tumor genome was sequenced in 2009. The International Cancer Genome Consortium (ICGC) has set its goal to obtain a full description of genomic, transcriptomic, and epigenomic alterations in 50 types and subtypes of cancer by sequencing over 25,000 tumors. Since it was launched in 2008, it has successfully sequenced over 7,300 tumors whose genetic map is available to any researcher in the world thanks to the Internet.

Spanish researchers have already sequenced the genome of 105 people with leukemia, and identified 78 genes related to this disease

The first results published by ICGC belonged to the Spanish group lead by Carlos López Otín from the University of Oviedo, and Elías Campo from the Hospital Clinic of Barcelona. The group deals with chronic lymphocytic leukemia, the most common form of leukemia. Spanish researchers have already sequenced the genome of 105 people with leukemia, and identified 78 genes related to this disease. Some of these genes are linked to more aggressive types of leukemia, so its presence in the tumor of a specific patient provides relevant information for prognosis.

This type of research corroborates James Coffin's words: In only fifteen years **"Biology has permanently associated itself with information technologies: Biology today is computational."**

Nanotechnology: When Medicine Talks to Cells

Nanotechnology allows atoms and molecules to be worked on and handled individually.

Nanotechnology covers the study, design, creation, synthesis, control, handling, and application of materials, devices and functional systems on a nano-scale, that is, a millionth part of a millimeter (10^{-9} meters), and thus allowing atoms and molecules to be worked on and handled individually.

To give you an idea: a hydrogen atom is one nanometer (nm), the diameter of hemoglobin is 5 nm, the size of a red blood cell is roughly 7,000 nm in diameter and 2,000 nm high, and the regular width of a human hair is 40,000 nm.

Nanotechnology opens new possibilities in medicine since devices smaller than 50 nm can easily fit inside most cells, whereas devices smaller than 20 nm can travel through the bloodstream. Some particularly interesting fields are those in monitoring (images), tissue repair, controlling the evolution of diseases, protecting and improving human biological systems, diagnosis, treatment and prevention, administering drugs directly to the cell, etc.

The scenario of opportunities for *in vitro* diagnosis includes detecting disease biomarkers with simple systems that confirm or dismiss pathologies in primary healthcare visits or consultations with a specialist, thanks to what is called "labs in a chip." Current *in vitro* diagnosis techniques barely account for 2% of healthcare spending. However, seven out of ten medical decisions are based on their data and have an effect on the treatment of choice, which entails a significant impact on the reduction of healthcare costs[8].

As these applications make their way to reality, nanotechnology offers advanced solutions, such as the ability to diagnose bovine spongiform encephalopathy ("mad cow" disease), or Creutzfeldt-Jakob disease in its hu-

[8] Spanish Nanomedicine Platform, Note for Innovation in Nanomedicine in Spain.

man form, before the affected animal or person dies, and even before the disease presents symptoms. The main barrier to developing a diagnostic method for the disease was the impossibility of distinguishing the human and animal functional prions from their infectious prion causing the pathology. These proteins barely generate any optical signals, so it is also impossible to detect them via traditional methods. However, they have been observed even in very low concentrations or in fluids, such as blood, by introducing gold nanoparticles that amplify the signal of the defective molecule millions of times[9].

Research on cell cultures has successfully inserted nanoparticles into cancer cells, illuminate them, and heat them with a laser, thereby killing the tissue.

The implications are clear. On the one hand, **it is possible to make a diagnosis before symptoms are present**. On the other hand, in the event that symptoms appear in an individual, it will not be necessary to euthanize all of the cattle on the farm, just the specimens with a defective prion.

The development of biosensors is also important in detecting tumor markers, since the ability to unmistakably distinguish the lack of a marker from trace-level concentration may be critical in diagnosing the presence of first-stage cancer—when the possibilities of applying corrective therapy are greater.

Therefore, a biosensor made up of gold nanostars of approximately 50 nm in size can detect PSA—the main prostate cancer marker—with sensitivity a billion times greater than the ELISA test normally taken in hospitals. The presence of this tumor marker after prostate cancer surgery indicates the relapse of cancer. Knowing it exists as soon as possible is important in the treatment process and in order to successfully defeat the disease[10].

From diagnosis to treatment. Research on cell cultures—not yet on live animals—has successfully inserted nanoparticles into cancer cells, illuminate them, and heat them with a laser, thereby killing the tissue. This photothermal therapy is based on particles covered by a biological substance that adheres to cancer cells by which treatment reaches single-cell precision and preserves the adjacent healthy tissue. The same structure used to amplify heat may contribute to detecting cancer, since they become sensitive to infrareds by anchoring to cancer cells[11]. If the tumor

[9] Proc Natl Acad Sci U S A. 2011 May 17;108(20):8157-61

[10] Nature Materials 11, 604-607

[11] Adv. Mater. (Weinheim, Ger.). 0935-9648 20, , 3866–3871 ((2008))

is detected at an early stage, its suppression may be approached before chemotherapy or radiotherapy become necessary.

BIND-014 is the first targeted and programmed nanodrug to enter clinical trials. It has been developed by researchers at the Massachusetts Institute of Technology (MIT), the Brigham and Women's Hospital, the Harvard School of Medicine and the company BIND Biosciences. Results in animals—published in April 2012[12] —show that BIND-014 can release seven times the amount of the docetaxel chemotherapeutic—used in prostate, lung and breast cancer, among others—in tumor cells without generating more side effects than the conventional administration of chemotherapy. By accumulating in tumors and not in healthy tissue, BIND-014 accomplishes a much more targeted treatment with greater efficacy.

BIND-014 is the first targeted and programmed nanodrug to enter clinical trials

Even though tests in humans are still under way, in the 2012 annual meeting of the American Association for Cancer Research, the results on the first 17 patients were presented. The first data of the study show that BIND-014 has an antitumor effect and is generally well tolerated. The reduction in tumors was achieved with substantially lower doses than with conventional docetaxel, which proves the greater efficacy of BIND-014 against tumors[13].

Mike Moradi, is founder and CEO of **Sensulin**, and an attendant to the XIX Future Trends Forum. He explained during the sessions how his company, Sensulin, is trying to develop a nanotechnological system to administer insulin. A patient with type 1 diabetes today needs to measure glucose—by pricking his/her finger and reading the result in a portable glucose meter—six to ten times per day, and self-administer a baseline dose of insulin every day with 3 to 5 more doses around meals. This may mean up to 16 daily interventions, and almost 6,000 per year, to keep the disease under control.

Sensulin has developed a nanotechnological platform to administer drugs—the Agglomerated Vesicle Technology—that imitates the pancreas and releases insulin when the body needs it and in the exact amount necessary to bring blood sugar levels back to normal. With this method, just one daily administration would suffice to cover the needs of the diabetic patient, and, as Moradi points out, "give them an opportunity to lead a normal life."

[12] Sci Transl Med. 2012 Apr 4;4(128):128ra39

[13] National Cancer Institute Bulletin, April 17, 2012 ▪ Volume 9 / Number 8

Nanotechnology reduces the doses necessary to achieve the desired effect and thereby reduce side effects

Nanotechnology increases the bioavailability of the drug in the human body, which reduces the doses necessary to achieve the desired effect and thereby reduce side effects. Based on a single daily administration and a single reduced dose, the cost-saving potential of this treatment can be easily imagined, considering the current market for insulin is $14 billion (estimated at $32 billion by 2018).

But the horizon of possibilities in this area is constantly growing. In the 2013 Work Program of the VII Framework Research Program, the European Commission proposes some lines of medical research in nanotechnology in the near future: the treatment of infectious bacterial diseases, biomaterials for advanced therapies and medical devices in cardiovascular and neurological/neuromuscular areas[14].

[14] European Commission C(2012) 4536 of 09 July 2012

Cell Therapy, a "Nobel Technology" with Long-Term Potential

Recent studies are opening pathways to explore the possibilities of induced pluripotent stem cells in the study of Alzheimer's disease

Cell therapy is a strategy based on the use of cells as a therapeutic tool. Its potential has been explored for decades with bone marrow transplants in leukemia cases, and now the discovery and characterization of stem cells in other body tissues (adult stem cells) have tapped into its potential. One more step was taken in 2006 when it was discovered that adult cells can be reprogrammed and can acquire the ability to become other types of tissues as in the induced pluripotent stem cells that earned Shinya Yamanaka, who discovered the technique, the Nobel Prize in Medicine 2012.

Basic research in this field is increasingly promising. One of its first applications is to obtain tissues that are difficult to extract from the human body and produce them in big quantities in order to study the molecular base of diseases. For example, researchers from the Imperial College of London have grown and analyzed stem cells from the blood of patients with von Willebrand disease, a disorder that obstructs clotting and affects one in every one hundred newborns. Thanks to this technique, an unprecedented amount of endothelium cells has been obtained from each patient to then analyze their specific conditions in detail, something hitherto impossible. In some patients, researchers have found new types of variations, which has fine-tuned treatments and reduced bleedings.

On a different note, researchers from the University of North Carolina at Chapel Hill have isolated adult stem cells from the human intestine, an objective that had so far eluded all scientific efforts. These cells are essential for understanding the mechanisms behind inflammatory intestinal disease, and possibly develop treatments for it and for the damage done by radio and chemotherapy in stomach cancer patients. Recent studies are opening pathways to explore the possibilities of induced pluripotent stem cells in the study of Alzheimer's disease and a hereditary heart disease called arrhythmogenic right ventricular dysplasia.

Cell therapy is already the object of quite a few clinical trials—particularly the autologous type, that is, the use of the patient's own stem cells, as explained at the XIX Future Trends Forum by **Bernat Soria**, director of the Andalusian Cell Therapy and Regenerative Medicine Program, and former Minister of Health in Spain. There are over eight-hundred trials

around the world, and at least 25 in Spain—classified by ClinicaTrials.gov, and some of them directed by Soria himself—on very diverse areas, such as limb and myocardial ischemia (both in diabetic and non diabetic patients), rectal fistulas, osteoarthritis of the knee, acute myocardial infarct, non-Hodgkin lymphoma, multiple sclerosis, or rheumatoid arthritis.

Cell therapy is already the object of quite a few clinical trials, that is, the use of the patient's own stem cells

The first FDA approval for a treatment of this type, says Soria, is recent: "Prevenge," an active cell immunotherapy against prostate cancer, was checked off in 2010. It is obtained by extracting white blood cells from the patient, treating them in a laboratory with a genetically modified protein to make them stronger against the tumor, and then re-introducing them into the patient's bloodstream.

Cell therapy—even though the regulation considers it a drug—raises some new problems for regulators, according to Soria. "The cell is not a substance the body can metabolize, just like traditional drugs; it is a live organism that interacts and may even change the phenotype. When regulators ask about the classic concepts of drugs, such as biodistribution, toxicity, or pharmacodynamics, it is hard to answer in classic terms. Cell therapy research also raises the question of whether the patent system is ready to protect intellectual property resulting from this type of studies."

From Genetic Knowledge to Prevention

Information on genetic predispositions is starting to become popular via services such as 23andMe. According to Esther Dyson, president of Edventure Holdings, even though findings on what genes and proteins intervene in diseases is constantly evolving, "this knowledge enables us to modify lifestyles and have an impact on our health."

However, Dyson points out that "information by itself will not change the behavior of individuals—take tobacco as a clear example—but other incentives are very effective. The very fact of knowing that you may influence the impact of an inherited genetic substrate on your health is a very powerful psychological incentive."

Findings on what genes and proteins intervene in diseases are constantly evolving

John Smyth, expresident of the European Society for Medical Oncology and Honorary Assistant Principal Cancer Research Development (University of Edinburgh), agrees with this perspective and adds that "governments are very interested in promoting preventive habits, since they would free up resources for health care and research in times of uncertainty and budget cuts."

James Coffin adds that lifestyle incentives are being introduced in the United States, for example, through corporate healthcare policies for employees, which represent 40% of coverage in the country. "In no few cases, to be entitled to one hundred percent of medical expense reimbursement, you have to comply with certain standards regarding body mass index (overweight and obesity), blood pressure, sugar levels, and no use of tobacco." According to Coffin, "the impact of disruptive technologies will pale by comparison with the patients' involvement in their own health."

Joel Kurtzman, Senior Fellow Milken Institute and managing director of Kurtzman Group, wraps up with another example: "there is an overwhelming number of drugs for diabetes. Their development places a significant burden on the system, specifically on resources, time, and research that could probably be alleviated with preventive measures."

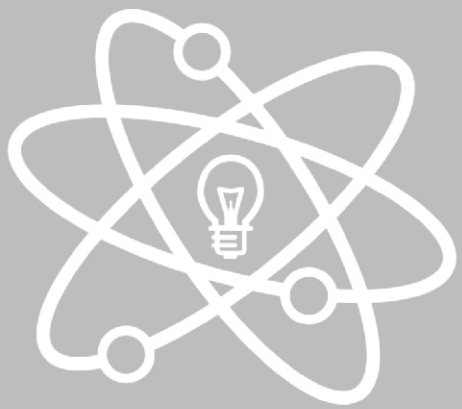
Chapter III. Resource Allocation and Innovation

Imagine the Future, and Make it the Present

Positioning Strategies in a Complex Environment

"Let's Deal with Diseases, Not Markets."

Patients Raise their Voice



Alpheus Bingham

CEO of Innocentive

Pharma Investment Decisions

The task assigned was to articulate the deal sourcing and selection criteria by which investment decisions in biotech and pharma startups are made. It goes without saying that how things ARE done and how things SHOULD BE done are not always in perfect correspondence. In fact, it is my feeling that the latter (the "should be") of these two topics is the one more important and salient to the goal of both investment success and biotech/pharma's long term sustainability.

The sourcing of investment opportunities is reasonably straightforward as those startup firms seeking investments are pretty actively soliciting for funds. That source of flow is typically coupled with a small team of lead generators actively creating a list of opportunities that are rapidly filtered to high potential candidates and reviewed by an appropriate investment board.

Addressing the final selection process with regard to HOW are investment decisions currently and typically made, I fear sheds little light on many underlying issues. The reader will learn very little to know that there is a focus on a skilled management team with a proven track record; or on the critical need for a compelling treatment hypothesis with either human clinical, animal model, or pharmacological indicators of success; or even, a focus on the necessity of establishing a market potential commensurate with the targeted returns on investment.

It may be supposed that such decision factors are common across many investors, many startup business plans and even many non-biotech sectors. What differentiates biotech/pharma investments from others? First, while all startups are "high risk" investments, biotech startups are not only high risk ventures for the reasons of effective execution, but the very underlying hypotheses are high risk in that many, which can be reasonably stated based on basic and sound biochemistry, fail to actually work in the clinical setting. Our command of human biology and all its complexity, is so lacking in a complete understanding that technical failure is as likely (or more likely) a biotech startup fate as execution failure.

Those who formulate a new treatment hypothesis are almost invariably too bullish on the probability of technical success. Their bullishness is often supported by intriguing early studies, a native enthusiasm, and a passion to improve the human condition. But those admirable characteristics are no guarantor of success as drug development failure after failure stands witness.

In reflecting on how pharma/biotech investments SHOULD BE made, I find myself reflecting on the counsel I have given both investors and startup founders over the years and acknowledge that the advice differs between the two. To founders, I would say that they need to find early opportunities for success and to capitalize on those early successes. To use the results of successful studies to articulate a clear and compelling story and to use that story to raise as much capital as quickly as possible. I advise this in the knowledge that the path will also be strewn with disappointments and that those disappointing events are NOT necessarily good opportunities to capitalize their businesses. And the capital raised will sometimes see them through the inevitable, and sometimes temporary, developmental setbacks.

Admittedly this advice would not be the same advice given to investors. I would counsel investors that the odds are often stacked against ultimate success in this complex endeavor and that instead of looking for early successes, they should look for early failures. If failure is the eventual endgame (and it more often than not is), investors should discover it as early as possible, when as little capital as possible has been consumed.

The history of drug development investments shows that large pharma companies manage the risk of individual projects by diversifying across large portfolios containing multiple disease targets, multiple therapeutic areas, multiple molecular structures and multiple pharmacological hypotheses. In a single biotech startup, this diversity is often minimized, in fact it is, many times: ONE pharmacology targeting ONE disease and with, at best, a handful of molecular solutions.

Nevertheless, should it not be true that, taken collectively, biotech startups would show positive returns? Unfortunately, taken as a whole, the biotech industry has a negative ROI and even many pharma companies today are struggling with inadequate returns on their complex portfolios.

The recommendations to front load successes (to founders) or to front load failures (to investors) is a fundamental difference in how the drug development plan for any given therapy is constructed. In spite of what seems, at first glance, to be contextually appropriate, albeit contradictory, advice, it is in the interests of the system's sustainabilities, that I would suggest that overall, the concept of front-loading FAILURE produces the best results.

In pharmaceutical startup investments, or even in internal corporate investments in individual projects, it is useful to think of capital as a resource for consuming uncertainty. An effective development plan is to identify the studies that resolve the greatest amount of uncertainty and conduct those first. This pushes your failures to occur earliest and delays studies likely to succeed until later in the development process. As uncertainty is 'consumed' the project either fails early or rapidly increases in its likelihood of ultimately succeeding. Thus as more capital is invested, it is invested in likely successful projects. While a single project may not survive as long under this scenario (clearly an interest of the founders), the overall portfolio success or investor success is optimized. And the ultimate consequences of false positives are a wasteful drain on resources for all stakeholders in the sector.

The practical consequence for investors is that they must delve deeply into the risk structure of the development plan, as opposed to

taking into account only the overall risk or probability of success. How this is done is crucial but outside the scope of this chapter.

The XIX Future Trends Forum dedicated a session to analyzing what criteria the public and private sectors were following in order to decide in what technologies and areas they should invest their resources.

The DARPA program of the US Department of Defense detects unmet needs, and tests novel ways of meeting those needs. Daniel Wattendorf, program manager at DARPA, presented on some current projects.

Let's deal with diseases, not markets

Big pharmaceutical companies spend—each year in total—about $50 billion in research and development. How do you combine the need to guarantee a return on investment with promoting pioneering technologies? Alpheus Bingham, CEO of Innocentive shared the keys and challenges in the near future.

"Let's deal with diseases, not markets." That is the solution William Haseltine, president of ACCESS Health International, suggests in order for big pharmaceutical companies to increase innovation, become

Imagine the Future, and Make it the Present

A little over 40% of new pathogens detected over the last twenty years are viruses, many of which have a high mutation rate

DARPA is a US Government agency established by the Department of Defense to promote basic research and technology-based projects that can be used directly in matters of national security. It touches upon several areas, from developing new materials to sensors and communications, as well as photonics, and of course, biomedicine.

One differential feature—as explained at the XIX FTF by Daniel Wattendorf, program manager at **DARPA**'s Defense Sciences Office—is that it **focuses on developing capabilities that are currently non-existent**. Another is its extraordinary flexibility in identifying interesting projects, establishing alliances to develop them, and granting funds—despite being a government agency. This is how DARPA may choose a big multinational pharma company, several biotechnological companies, and university research labs as partners. Oftentimes it works simultaneously with all three of them.

This is the case with DARPA's interest in vaccine development. A little over 40% of new pathogens detected over the last twenty years are viruses, many of which have a high mutation rate, as proved by the H1N1 pandemic in 2009. Creating new vaccines is a years-long process. A promising attempt at developing DNA vaccines began two decades ago, but it has not yet translated into available clinical products.

For this reason, DARPA has chosen RNA (as opposed to DNA) to start a new vaccine production methodology. Research is yet in the experimental stage. It is being conducted by an alliance of a multinational pharmaceutical company (Sanofi Pasteur) and two biotechnology companies: the German CureVac and the French In Cell Art, which both specialize in RNA technologies.

Genes act by transcribing DNA into messenger RNA (also called mRNA), which in turn is translated into a protein, which carries out the function of the gene. The advantage of using RNA is that it is closer to the protein—which is essential for the immune system to successfully react to the pathogen—and since it carries out the transcription, it allows immune-modulation in cellular mechanisms, giving the vaccine its protective effect.

Preliminary studies in animal models[1] show that RNA is suitable for the development of vaccines against active virus chains—that is, chains that are currently in the environment and not the result of past mutations, as is often the case with the flu. These vaccines shall be mass-produced in a short time frame, which is essential when reacting against new and very virulent pathogens. Furthermore, these new vaccines are kept at room temperature, a very rare characteristic nowadays and one that facilitates storage, distribution, and use.

Blood Pharming: The goal is to develop a portable device that produces universal donor blood from parent cells on the spot, which would transform the blood supply for transfusion.

Blood Pharming is another innovative DARPA project. Nine institutions are part of this project, including the biotechnology company Celgene, the University of Loughborough in the United Kingdom, the Massachusetts Institute of Technology, and the Cleveland Clinic (the latter two are both in the US). The goal is to develop a portable device that produces universal donor blood from parent cells on the spot, which would transform the blood supply for transfusion. One problem with blood is that its multiple components (red blood cells, platelets, and plasma) expire with time, making a constant flow of donations necessary. The challenge is greater when the blood needs to be taken to war-zone areas: transportation not only reduces the lifespan—because of the time it takes—it may also alter the quality if strict rules for conserving the blood are not followed.

Once again, **the DARPA approach stands out by stepping away from the trend**. It uses genetically engineered red blood cells, since they have a relative advantage over embryonic stem cells and induced pluripotent cells (IPSC). The truth is that red blood cells yield better results in availability, cost-effectiveness, security—embryonic cells are oncogenic and IPSC might be too—, and pharmacokinetics.

In the United States, 70% of the population say they are willing to take part in clinical trials, but only 6% of the population with severe or chronic diseases do so. Out of that 6%, over two thirds are in big city hospitals. The lack of patients makes clinical trials more expensive. Costs would reduce considerably with more candidates in stage III, especially if they could be properly chosen with biomarkers.

However, the main practical barrier to participating in trials is that you need to live near a healthcare center, or be able to travel to one to take your samples. This is the case even in the most advanced models. To give

[1] Protective efficacy of in vitro synthesized, specific messenger RNA vaccines against influenza A virus infection," Nature Biotechnology, November 25, 2012.

In the United States, 70% of the population say they are willing to take part in clinical trials, but only 6% of the population with severe or chronic diseases do so.

you an example: REMOTE (Pfizer) was launched in 2011, and it is the first at-home clinical trial conducted in the United States. Patients are recruited via the Internet and they sign up through an online platform. Drugs are home delivered and patient data are uploaded to the digital platform via a computer or phone call. However, the blood for the biochemical follow-up is still extracted in clinical analysis laboratories.

DARPA has launched a project to transition away from filter paper that is traditionally used to collect blood samples for the heel stick test (to detect congenital metabolic disorders in newborns). The goal is to obtain a format sensitive to many more indicators that can be mailed to the corresponding laboratory so that less blood would be needed for assessment and follow-up purposes. The patient could extract his/her blood at home with a finger prick similar to measuring blood sugar levels in diabetics; it would not require special conservation conditions and it could be mailed, so the trial methodology would be completely at-home this time. Such a system would exponentially multiply the number of real candidates in trials, which would subsequently have a positive impact on the cost of developing new drugs.

Positioning Strategies in a Complex Environment

Synthetic biology and cell therapy may roll in with the next innovation wave

Over the 25 years **Alpheus Bingham** worked at Eli Lilly, he held high-level positions throughout all the drug development stages: from strategic planning to managing the product portfolio and establishing research alliances. He was vice-president of R&D Strategy, Innovation, and e.Lilly. Today he pioneers open innovation and collaborative approaches to R&D: he is co-founder of Innocentive and member of the advisory board of the MIT Center for Collective Intelligence and the Business Innovation Factory, as well as visiting scholar at the National Center for Supercomputing Applications at the University of Illinois. His career puts him in a privileged position to analyze some of the current challenges in drug development from a private sector standpoint.

In the United States, says Bingham, **the pharmaceutical industry invests $50 billion per year in R&D, approximately. The Government spends just as much through its various agencies, while venture capital companies spend $10 billion through biotechnology firms.**

"Of all the disruptive technologies, biomarkers are particularly appealing to big firms," says Bingham. **"Synthetic biology and cell therapy may roll in with the next innovation wave, but they are less developed today."**

How can companies position themselves to get a head start in these new fields without risking their investment beyond what is reasonable? "There are different ways. Sometimes, alliances with university research laboratories are forged. Or a venture capital company is incorporated to invest in institutions that are testing new hypotheses or experimenting in new fields. This is typical in synthetic biology in that when you are a member of an executive board, you are keeping abreast of progress. If the potential of a new technology is confirmed, you may take steps to increase your stake in the company."

New questions also arise with new technologies. **Biomarkers raise the question of whether the current business model leaves room for personalized medicine**, where drugs adapt better to patients—increased efficacy and reduced side effects—**but their market share decreases the more specific they are.** In the words of Alpheus Bingham: **"If there are**

ten new drugs for what used to be treated with one, the price will increase to offset greater development costs and a smaller number of patients."

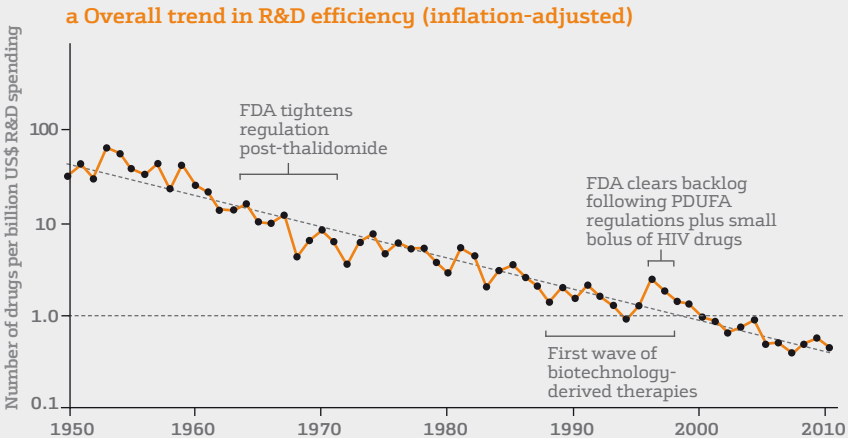
However, **William Haseltine** says that **"it is estimated that thirty percent of patients do not fully comply with the treatment: they quit the therapeutic plan before finishing it."** This phenomenon is partly due to the collateral effects drugs entail.

Esther Dyson, president of EDVenture Holdings, highlights that **"since personalized medicine improves drug design, it will reduce toxicity. Therefore, therapeutic compliance, along with sales, will increase, which will contribute to companies amortizing costs."**

According to Elvira Sanz, president of Pfizer Spain, there is no doubt that **"pharmaceutical companies are strong backers of personalized medicine through biomarkers**. But we are experiencing a transition period where we will have to continue developing less specific drugs while finding a way to fund the quality-leap in research."

Alpheus Bingham points out a trend that is bluntly shown by data: **the number of approved drugs per million invested in R&D by the pharma industry is increasingly lower.**

Personalized medicine improves drug design, it will reduce toxicity, along with sales, will increase



Nature Reviews Drug Discovery 11, 191-200 (March 2012).

Something else needs to be the transformational element: changes to the structure, organization models, and the way R&D is conducted…"

"This downward trend in research productivity is just as sharp when you break down the graph into decades. Over the last seventy years, medicine has experienced vast technological and pharmacological progress: nothing manages to alleviate or reverse this phenomenon. New technologies are not the answer to this problem. Something else needs to be the transformational element: changes to the structure, organization models, and the way R&D is conducted…"

This is precisely the answer that William Haseltine tried to suggest at the XIX Future Trends Forum when the problem was first addressed.

"Let's Deal with Diseases, Not Markets."

William Haseltine, President and CEO of ACCESS Health International, knows very well the multiple stages of drug development, from basic research to product marketing. He has been a professor at Harvard, pioneered research on HIV, founded the Division of Cancer Pharmacology and the Division of Human Retrovirology at the Dana-Farber Cancer Institute, co-founded the Human Genome Sciences company and other biotechnological companies, and authored more than two hundred scientific papers and several books. He excels at unifying the standpoints of a biotechnology researcher and a businessperson. Today, he chairs ACCESS, a non-governmental organization based in Singapore, the Philippines, India, Bangladesh, the United States, Sweden, and Indonesia that promotes equitable access to health care through projects that have an impact on funding, provision of services, and technology.

Today's pharmaceutical business map is made up of a few big companies with a turnover ranging from $50 to $100 billion per year with drug-sales between $5 and $10 billion.

Haseltine describes in broad strokes how **today's pharmaceutical business map is made up of a few big companies with a turnover ranging from $50 to $100 billion per year with drug-sales between $5 and $10 billion.**

However, says Haseltine, this was not always the case: "There used to be many more smaller companies. **Problems related to a return on investment and R&D productivity faced by the industry today are, I think, for the most part due to their size."**

He encourages us to reflect upon the pressure exerted on multinationals to market drugs that generate between $2 and $5 billion in revenues, and how, in the last few years, this came to be based on the **"me too drugs"**, that is, **drugs with a very similar structure to those we already know, but that prolong a patent's life span by introducing minor pharmacological changes**. So when the patent expires, there is a successor ready that does not necessarily include great therapeutic innovation. "This strategy is being examined by authorities that approve drugs and decide what drugs are publicly funded. We must realize that science is not mainly designed to satisfy the needs of markets," says Haseltine. Some of the greatest fiascos of the last twenty years come from trying to transform a drug that works well for a specific need into, let's say, a painkiller with a much broader spectrum.

Therefore, he proposes going back to basics: **"Let's deal with diseases, not markets."** How does this translate into terms of a business structure? **"Creating small companies made up of no more than five to ten people**: clinicians who know the disease, researchers that master the biological basis of the disorder, etc.; people with a profound understanding of the problem and that are very capable of detecting nuances, subtleties that oftentimes have the answer to a problem in experimental results."

Create small companies made up of no more than five to ten people while big companies acting as a virtual structure that provides funding and technical assistance

To maintain that concentrated and united talent throughout the process, Haseltine stands for **big companies acting as a virtual structure that provides funding and technical assistance**, creating holdings with many small companies depending on them, each of which would be focused on developing a drug for a specific clinical need.

"This system could reduce the cost of developing a drug to at least a third. There are good examples showing that this staff management and investment structure markets drugs under $100 million while obtaining a return ten to fifteen times greater, even without a blockbuster," says Haseltine.

Furthermore, the greater the action range of a drug and, consequentially, the greater the number of people potentially benefitting from it, the more patients regulators require in trials to guarantee both the efficacy and safety of the active principle, which makes the process more expensive for companies. As Elvira Sanz, president of Pfizer Spain, pointed out in this respect, "small is smart."

Patients Raise their Voice

Patients have gone from being passive subject to creating organizations that give their pathology visibility and make them stakeholders in the decision-making process

Over the last few decades of the 20th century, drug research and development strategies are being enhanced with a new, very active player: **patients**, who **have gone from being passive subjects,** receiving individual care and unconnected to each other, **to creating** organizations that give their pathology visibility, give them a say in the public discussion, and make them stakeholders in the decision-making process.

The Spanish Federation of Rare Diseases (FEDER by its Spanish acronym), is a paradigmatic example. Its director, **Claudia Delgado**, presented on their history at the XIX Future Trends Forum. **Rare diseases affect less than 5 individuals in 10,000 inhabitants.** Low prevalence complicates diagnosis, and makes them less interesting for the pharmaceutical industry—since they do not have critical mass to become an appealing target market—and leaves them on the margins of the political agenda.

However, according to the World Health Organization, **the aggregate of rare diseases affects 6% to 8% of the world population**, that is, 500 million people. For the 3 million affected people in Spain, the connectedness among them transforms a marginal phenomenon into a group with shared issues and, above all, the power to demonstrate in large numbers.

FEDER, founded in 1999, has chosen precisely this approach, and today it gathers 230 organizations with the goal of building a strong community of groups and patients living with rare diseases, to be their voice, and to fight, directly and indirectly, to alleviate the impact of these pathologies.

Claudia Delgado says that "it is not just about getting the drugs, it's also about a holistic, long-term approach to treating these pathologies." Real access to diagnosis is a priority for FEDER and Eurordis—the European network of rare diseases. In many cases, from the onset of the first symptoms, it takes ten years to reach a diagnosis. Those are ten years of pilgrimage through health care that are rife with uncertainty and frustration for patients and their families. The problem is made worse by the fact that 60% of these pathologies are severe, degenerative, or impairing, and half of the cases appear in childhood. A well-known example is amyotrophic lateral sclerosis, suffered by the physicist Stephen Hawkings.

Delgado believes "establishing specialized centers and a national and international network that offers a multidisciplinary approach" is the key to pro-

The European Union itself has established some pillars to guide its actions on rare diseases

gress in diagnosis and treatment. Precisely because the individuals affected are dispersed geographically, there is a need to "standardize data collection and have a network of biobanks in order to make sample collection, analysis, and study a reality. We need cross-country registries of cases to track the epidemiology of these disorders more accurately, and to promote broad research strategies."

The European Union itself has established some pillars to guide its actions on rare diseases. The first being that each country must have relevant national plans and strategies. **Out of the roughly seven thousand rare diseases, only one thousand are known in some detail**, so the EU proposes defining, coding, and listing them. The EU is also an advocate for reaching a Europe-wide expert consensus that will facilitate the collective evaluation of orphan drugs—those that treat this type of diseases—; establish verified guidelines for newborn screening and early genetic diagnosis for detecting the disease, or the risk of suffering it; and set standard criteria for diagnosis and care.

Claudia Delgado concludes by saying that "to transform research into new therapies, we need more funds for basic, applied, and translational research. We need to develop public-private alliances, provide training on rare diseases to researchers, and accomplish Europe-wide data exchange."

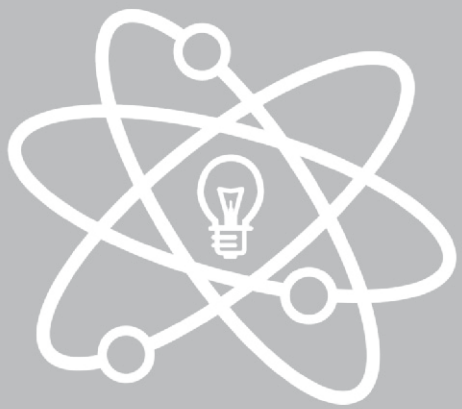
Chapter IV. Academia-Industry Alliances:

Academia-Industry Alliances: An Open Innovation Model

A System where Everybody Wins

Redesigning Trials to Increase Efficacy and Reduce Costs

Patent Rights and Open Innovation



Emilio Mendez

Director of the Center for Functional Nanomaterials of the US Department of Energy, Prince of Asturias Laureate for Scientific and Technical Research (1998), Trustee of the Bankinter Foundation of Innovation.

Previous chapters have made it abundantly clear that one of the biggest roadblocks to the discovery and development of new drugs is the overwhelming cost of the whole process, from discovery to commercialization, which in some cases exceeds one billion dollars. As a consequence of this huge cost, the price of specialized drugs can be prohibitively expensive – especially when they serve small groups of patients – during the limited number of years the developing companies have before their patents expire and the drugs become "generic." In turn, the elevated price is passed along to the patient, and eventually to the healthcare system, be it public, semi-public, or private. This is occurring at a time when, everywhere, the need to curb costs and reduce budget deficits is imperative.

How then to discover and develop new drugs more cheaply? This is one of the key questions addressed in this Future Trend Forum. The pharmaceutical industry is exploring a variety of approaches, some of them similar to those that have been followed before by other large-investment industries such as the microelectronic industry, most notably, the formation of partnerships or consortia of a number of companies for development of technologies in their pre-competitive phases. This panel discusses another approach: the collaboration between universities and pharma companies, which, as discussed here, can take different forms, but in all cases it exploits what each of the two types of organizations does best.

The main mission of the university is to transmit existing knowledge and to create new one. Discovery is thus inherent to the academic world. Development, on the other hand, consists on applying rele-

vant knowledge to the creation of new products or processes that serve society's needs, whether real or perceived. Because this is the scope of industry, development occurs most naturally in companies. Academia and industry seem then natural and complementary partners, and in an implicit or perhaps unconscious way they have been for a long time: basic knowledge generated at universities has been applied to develop commercial products, including drugs. But this traditional separation of "tasks" has its limits. First, the transfer of usable knowledge is slow, at least for the pace of rapidly moving industries that a fast-evolving society demands. Second, it is inefficient, in the sense that a considerable fraction of the knowledge created by universities does not have a "monetary value." Third, it is "leaky," in that the economic benefits of investing in academic research in one region or country are frequently reaped even by far away countries.

More active and effective models of interaction between universities and corporation are surging all over, especially in fast-pacing and cost-intensive industries, and in particular in the pharmaceutical sector. In the past, in the most dynamic scenario, companies subcontracted academic research groups for specific projects and universities licensed patents. In the near future, as Prof. M. José Alonso explains, in addition there will be synergistic collaborations such as the Enlight Biosciences Project that involves universities, hospitals, and big pharmaceutical companies, and consortia such as TRANS-INT that include small companies, besides universities and large firms.

These new models of interaction will bring benefits to both academic and industrial institutions. They will give academic research a tangible sense of value and enhance its visibility in society, and will diversify the sources of funding for university research. This kind of alliances benefit industry too: they create partnerships with the most qualified scientists and give access to advanced instrumentation and techniques, while offering industry an excellent opportunity to steer scientists' creativity in directions of commercial interest. Not less important is the training and emergence of a new generation of scientists attuned to society's needs and with a heightened awareness of corporate culture. Many of them could end up working in industry and become the natural links with the university, thus assuring the flow of ideas in both directions.
Although not mentioned by the panelists in the course of their presentations, a word of caution in this rosy scenario is warranted, though. If unchecked, a very close research alignment between university and industry runs the risk of blurring the core mission of the university, which

is educational, first and foremost. In addition, an excessive reliance of academic researchers on industrial contracts might compromise their independence and impartiality, thus jeopardizing the prestige and reputation for integrity that scientists enjoy. Finally, an emphasis in the university on practical research at the expenses of curiosity-driven science, although perhaps beneficial to society in the short run, eventually would dry the scientific creativity from which spring the fundamental breakthroughs on which future practical advances rest. Clear rules and adequate oversight by the universities would drastically reduce those risks and make their partnership with the pharmaceutical industry a true win-win proposition.

Academia-Industry Alliances: an Open Innovation Model

Now, more than ever, the demand for truly transformational therapies and increasing development costs call for an association between university research centers—commonly known as academia—and the pharmaceutical industry, for the benefit of society as a whole[1][2]. In academia, the industry scouts for talent, learns about new research trends and experimental techniques with a groundbreaking potential; and in the industry, academia finds tools to transform its ideas and paradigm shifts into products.

In academia, the industry scouts for talent, learns about new research trends and in the industry, academia finds tools to transform its ideas and paradigm shifts into products.

The XIX Future Trends Forum allotted some time for analyzing barriers and opportunities in aligning knowledge and industry, in a round table facilitated by **Emilio Méndez**, Prince of Asturias Award for Scientific and Technical Research (1998). He is the Director of the Center for Functional Nanomaterials of the US Department of Energy, and Trustee of the Bankinter Foundation of Innovation. The keynote speakers were two internationally renowned scholars and researchers: María José Alonso from Spain, and John Smyth from Scotland.

María José Alonso is a scientist and a professor at the Department of Pharmacology and Pharmaceutical Technology at the University of Santiago de Compostela, and in Spain she has pioneered the application of nanotechnology to drugs, a field where she has conducted research not only at USC but also at *Université Paris-Sud* and the Massachusetts Institute of Technology (MIT). From 2006 to 2011, she was vice-president of Research and Innovation at the University of Santiago de Compostela. Her research has attracted the interest of organizations such as the WHO and the Bill and Melinda Gates Foundation, and has been reflected in twelve patents, eleven of which have been licensed to the pharmaceutical industry.

[1] Melese T, Lin SM, Chang JL, Cohen NH, Nat Med. 2009 May;15(5):502-7

[2] ICSU Committee on Freedom and Responsibility in the conduct of Science, Scientific Relations Between Academia and Industry: Building on a New Era of Interactions for the Benefit of Society (workshop report, July 2012)

University spin-offs are arising and the number of registered patents is increasing.

"Many of the ideas that add value to drug discovery come from academia. But it is also true that many other ideas are lost along the way and end up coming to nothing. The reason behind this is that there are many barriers to overcome," points out Alonso.

A researcher cannot just have an idea, she says; **he/she also needs "a strategic approach, that is, what do I want to do with this idea?" The next step is "becoming visible enough:** getting published in the most relevant magazines, and if possible, obtaining intellectual property rights. But this does not depend on the researcher alone, but also on the institution they work for, the university ecosystem where the latter is embedded, and even the country. If you have enough visibility, raising funds will be much easier. In any case, at this point, you need to take a step further: **collaborate with a company, create a startup, etc.** You cannot continue on your own as a scholar."

Alonso regrets that **collaboration in Spain is**, in many cases, **still passive:** academia is merely contracted by the industry. Even so, she acknowledges that **"university spin-offs are arising, although it is still a minor phenomenon," and "the number of registered patents is increasing."**

From your perspective, what does the future hold for this relationship? "I see a model of synergies in the future—it is already starting to be evident in no few cases. The **Nestlé Institute of Health Sciences** being one example, but there are others, such as the one promoted by the **Karolinska Institute** and **Astra Zéneca**. These initiatives will have a huge impact."

"There are other synergy models that do not require new headquarters, such as consortia. For example, **Enlight Biosciences** in the US created by several pharmaceutical multinationals and relevant researchers from Harvard, the MIT, and the big hospitals in the Boston Area… Their goal is to create knowledge and patents, based on which, startup companies can develop products," says Alonso.

There are other systems, such as the **cross-border research consortia promoted by the European Union**. Alonso is coordinating an international project approved in 2012 by the European Commission under the title "new oral nanodrugs: transportation of macromolecules through the intestinal barrier" (TRANS-INT). Funded with €11 million, it seeks to develop a nanodrug candidate in five years to effectively fight diabetes. There are "16 institutions, including cutting-edge academic laboratories, small companies, and big pharmaceutical companies such as the multinational Sanofi, among others."

John Smyth is an honorary professor of Medical Oncology at the University of Edinburgh. His career combines teaching, research, clinical practice, and a detailed knowledge of the drug approval process. He has been a medical doctor for forty years, twenty of which were at the helm of an integrative cancer care center, and he has promoted drug development both from his university research center and from trials with patients. He is the author of over 300 papers in journals subject to peer-review, he has been Editor-in-Chief of the European Journal of Cancer, and presided over the European Society for Medical Oncology and the Federation of European Cancer Societies (today the European Cancer Organization). He is presently part of the advisory expert group on oncology for the European Medicines Agency (EMA).

The academia-industry association "is the way to go, but there is a lot of room for improvement

Smyth is convinced that **the academia-industry association "is the way to go, but there is a lot of room for improvement."** Moreover, the industry solves a practical problem: postdoctoral researchers in universities usually have three-year grants to become involved in a project. What happens when this time elapses? Ending the relationship of a researcher working on a gene, a biomarker, or a new molecule in a long-term project is a "clear disincentive. But if a pharmaceutical company is funding the project together with the university, the transition from a three-year grant to a five to ten year relationship under their partnership is much easier," says Smyth.

A System where Everybody Wins

Alliances between academia and industry are beneficial for both sides.

Advantages for academia:

- Ensuring knowledge gained will become a product, with the resulting benefit for society
- Enabling the development of better, far-reaching, fundable research plans
- Tapping into financial and technological resources
- Providing greater visibility to academic research, which in turn generates greater support from administrations and society

Advantages for the industry

- Academia provides highly qualified researchers
- Access to long-term independent research
- Access to ideas with the potential to generate marketable new paradigms
- Access to next-generation knowledge to approach specific problems
- Obtaining a global view of research trends
- Collaborating with highly trustworthy players in society

Smyth is concerned with two issues where he has great expertise. The first one is that **"a scenario where developing a drug takes from seven to ten years and costs around $1 billion is not sustainable."** The second: **"The regulator is not the bad guy**. Their role is honest and transparent, and it consists in saying: **'Prove to me the efficacy and safety of this drug.'** But oftentimes this is not possible, because the studies upon which authorization requests are based are poorly designed from the start."

Clinical trials are usually divided into five stages. The preclinical stage examines the efficacy of the compound against the disease in animals or lab samples. The vast majority of scientific studies that correspond to this stage are publicized by mass media as progress in terms of new knowledge, or possible new treatment for diseases.

Stage 1 is carried out on healthy people. Their goal is to establish whether the substance is safe and what the dosing range is without prohibitive side effects. Absorption, metabolization, and elimination of the compound by the organism are also studied in terms of how long its effect lasts and what the best administration is (oral, IV, etc.). In the case of cancer, stage 1 is carried out on sick people.

The bulk of the investment in drug development is focused on stage 3. If successful, the drug will be presented to regulatory authorities for its approval.

Stage 2 tests the drug in patients who already suffer from the disease (generally between 40 and 60) since it is an initial, detailed analysis of the molecular efficacy against the pathogen. Depending on the case, different doses and side effects are evaluated, and how the disease, symptoms, or both improve.

If the treatment passes the testing in animals, healthy individuals, and a limited number of patients, then it moves on to **stage 3**. Typically, some 3,000 patients take part in this stage that extends over three years. The objective of this stage is to confirm both efficacy and possible long-term side effects. Depending on the type of trial, a group of patients will receive the new treatment and the best treatment available to then compare results. If there is no treatment, the other group normally receives a placebo. **The bulk of the investment in drug development is focused on stage 3. If successful, the drug will be presented to regulatory authorities for its approval.**

Stage 4 takes place when the drug has already been marketed, and it consists of analyzing potential long-term side effects in big populations. Moreover, it may be used to test new indications for the drug, that is, test its efficacy against other diseases.

Redesigning Trials to Increase Efficacy and Reduce Costs

John Smyth proposes changing the model--as José María Fernández Sousa, president of Zeltia mentioned as well--and "making the most out of the preclinical stage," since "we can now work with human tissues, and that is essential. Moreover, biomarkers provide reliable information on what will or won't work further on."

Furthermore, he proposes changing stages 1 and 2 to exclude selective experiments in a few patients, and instead, carry out "intensive research with multiple groups and an adaptable design as initial results are obtained." This methodology would enable reaching the traditional stage 3—known as "pivotal studies," since they are key for future approval—with "fewer but better selected patients, which would improve the quality of results and reduce costs drastically."

This expert referred to studies underway that have adopted this new approach. Such is the case of I-SPY 2 a clinical trial on breast cancer in the United States promoted jointly by the FDA, the National Cancer Institute, the Foundation for the National Institutes of Health, the Biomarkers Consortium, and no less than eleven academic research centers, several pharmaceutical companies, and patient representatives.

Change the model and make the most out of the preclinical stage, since we can now work with human tissues.

Where a traditional trial seeks a large number of patients under the most similar conditions possible so that differences do not bias results on the drug's efficacy, the new approach uses genetic profiling to look for detectable differences with biomarkers that can distribute patients in different groups and assign the drug that initially seems the most beneficial to them.

Therefore, if there are forty to sixty patients for a first efficacy analysis in stage 2 of a traditional trial, in stage 2 of the I-SPY 2 there are almost five hundred patients involved, divided into six groups; and, based on their genetic profile, they are assigned to conventional therapy or conventional therapy plus one out of five new drugs, which are precisely the ones being tested. As results arrive, patients who gradually join this stage will receive treatment that is further adjusted to the genetic profile revealed by their tumor biomarkers. At the end of this stage, seven hundred patients will have been studied, and drugs with poor results will be eliminated. Only drugs with proven efficacy will move onto stage 3—the pivotal study.

The success rate of the traditional stage 3 is 30% to 40%, the new design is estimated to be 85%.

Thanks to the intensive, adaptable design of stage 2, the pivotal study will require just three hundred patients instead of the usual three thousand patients, precisely because their genetic profile increases the value of the information provided by the tests. Furthermore, where **the success rate of the traditional stage 3 is 30% to 40%, the new design is estimated to be 85%.** Fewer patients with greater success probability and a stricter methodology will result in shorter authorization time frames and also significant cost reduction throughout the process.

Patent Rights and Open Innovation

In open innovation agreements it must be absolutely clear from the start who will hold intellectual property rights and what can be licensed by whom.

"The collaborative model is based on sharing information and, therefore, requires an intellectual property system very well designed to protect the results of this joint effort with patents," says **Tim Andrews**, partner in Marks&Clerk, a British law firm specializing in patent rights.

"In open innovation agreements it must be absolutely clear from the start who will hold intellectual property rights and what can be licensed by whom. This is essential to guarantee trust between the parties," he says. An initial method to weight the potential of such collaboration would be "confidentiality agreements to access information each party may have at that moment."

Patents are a cumbersome and expensive procedure. Tim Andrews believes the **joint patent system is progressing strongly in Europe. Costs will be reduced because rights will centralize on one single patent and claims in only one court, which will have its base in London.** "The not so good news is that it will not come into force until 2020."

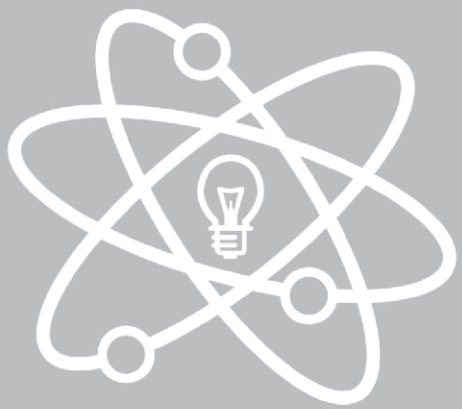
Chapter V. The Role of Startups in Innovation

Venture Capital and the Pharma Industry Take a Step Backwards

Proposals to Lure Investment to Start-ups

Patients, a Key Player

Innovation Inhibitors and Accelerators



There was a discussion at the XIX FTF regarding the role of startups as a source of R&D and innovation in drug development. Mike Moradi, Richard Kivel, and Patrick Flochel took part in the discussion led and facilitated by Esther Dyson.

Mike Moradi

Founder and CEO of Sensulin, a company developing nanotechnology techniques to meet the insulin needs of diabetics with one daily dose only. Sensulin is Mike Moradi's 8th startup. He has, among others, co-founded Charlesson, which discovers new ophthalmology drugs, and in 2009 was ranked as the number one pharmacological development company in growth pace. Other milestones in his career are NanoSource Technologies, acquired by DuPont in 2002; Unidym, purchased by Wisepower in 2011; and SWeNT, the first manufacturer of one-layer carbon nanotubes.

Richard Kivel

Senior Manager at Bridgewater Associates. With $120 billion, Bridgewater Associates is the largest investment fund worldwide. Kivel's career has been driven by his experience as an entrepreneur in international technology and biotechnology companies such as Rhapsody Biologics, among others, that is developing next generation vaccines; TheraGenetics, specializing in pharmacogenetic diagnosis tests and central nervous system pathologies; or MolecularWare, a spin-off from the Massachusetts Institute of Technology that became a global leader in microarray technology. He has been president of the Global Board of Directors of the MIT Enterprise Forum. Richard Kivel is also a Trustee of the Bankinter Foundation of Innovation.

Patrick Fochel

Global Leader for the Pharmaceutical Industry at Ernst & Young, a company where he has also held the position of Life Sciences Leader for Europe, the Middle East, India, and Africa. He is part of the creative team at the Ernst & Young Global Life Sciences Center and has solid experience in assessing biotechnology, pharmaceutical and healthcare technology companies.

Esther Dyson

President of **EDventure Holdings**, has broad experience as business angel and investor. She is well known for her participation on Flickr and Del.icio.us. One of her areas of interest is preventive medicine and potential applications resulting from big healthcare data, hence her collaboration with companies such as 23andMe, PatientsLikeMe, VitaPortal, Sleepio, Genomera or PatientsKnowBest, among others.

"The fact that Viagra was one of the latest successfully developed drugs by big pharma companies under the traditional model proves that the scenario is changing. The active principle started in the trial as a drug against hypertension, but a peculiar and unexpected side effect made it a star against erectile dysfunction. **For a few years now, new drugs approved by the FDA actually come from laboratories and university research centers and startups, although it is true that many have evolved into big biotechnology companies,"** says Mike Moradi.

How does this model actually work? Moradi says that "it typically starts in a university laboratory, paid for with public subsidies or private foundations; the technology is developed as much as possible with those funds, and then they try to get the support of a business angel for the first clinical trials. Finally, if things go well, who knows, maybe there will even be an alliance with a big pharmaceutical company..."

For a few years now, new drugs approved by the FDA actually come from laboratories and university research centers and startups

Moradi is convinced that "this model will become more frequent because it is very efficient, as **William Haseltine**, President and CEO of ACCESS Health International, has mentioned over the previous sessions. However, if things turn out badly, it is easy to wind-down the company at the right time before spending tons of money in frustrated development. In most cases—and everyone has this type of failure in their entrepreneurial portfolio—you will have invested only public funds, or funds from a business angel.

Venture Capital and the Pharmaceutical Industry Take a Step Backwards

Richard Kivel shares the point of view of investors: **"Life sciences are obviously appealing to markets. The issue is that money goes to projects in very advanced stages. In 2011, nearly $5 billion were invested in our industry through 450 operations, but only 125 investments went to projects in their initial stages**, the rest was allocated to projects with five to ten years of progress made. And this is frustrating, because **there is huge potential in new technologies that may never end up seeing light because they didn't make it to the next funding round."**

One problem is that **the return on investment cycle "is ten years on average, whereas some promising healthcare technologies have fifteen to twenty-year cycles."**

That the return on investment cycle "is ten years on average, whereas some promising healthcare technologies have fifteen to twenty-year cycles

How are startups seen by pharmaceutical multinationals? Having profound knowledge in the field, Patrick Flochel points out the difficulties in the environment. **"Big companies earned $40 billion less in 2012 because of patent expiries—add that to the price adjustments made by governments in times of crisis of up to 6% in the Euro Zone.** On a different note, **emerging markets**—object of great expectations—**are growing at a slower pace than expected: 12% in 2011, but below 7% in 2012."**

This complex environment calls for cautious investments across the board, which affects funds allocated to innovation: **"Over the last four years, the capital invested in biotech companies by the 28 biggest pharmaceutical and biotechnology companies worldwide has reached a plateau at $16 billion. In 2011, advances were cut by 64% compared with 2009**. Companies are also entering the flow much later: almost in the last stage of trials or when there already is a product approved by the FDA or the EMA. Moreover, multinationals are no longer pharmaceutical companies, now they have rebranded themselves as healthcare companies, because they are part of the healthcare system and they are required to contribute to it. **Financial markets are putting a lot of pressure on them, which makes them take fewer risks and invest in activities that are less uncertain than R&D**, such as generics, vaccines, emerging markets... **The healthcare system also** adds more pressure in that **it wants pharmaceutical companies to produce measurable healthcare**

results. And the industry, in turn, passes this pressure onto innovative companies."

The growing involvement of multinational companies in the sustainability of the healthcare system is manifest in their investment in areas closely related to cost- saving, as Flochel points out: "Ways of increasing patient compliance to treatments, promoting preventive lifestyles, boosting telemedicine. This takes resources away from investing in drug development through budding companies."

Given this context, Kivel believes public support for research will continue to be essential. **"The good news in public funding is that it seeks to promote scientific research: it does not expect a return as an investment partner would."** The flipside is that "public administrations do not always get it right when allocating funds because they do not take the market into account. Striking a balance is hard. However, there are some privately-funded institutions successfully striking such a balance, for example, **MIT's Deshpande Center**, or similar foundations in **CalTech**."

The good news in public funding is that it seeks to promote scientific research: it does not expect a return as an investment partner would

For example, in its latest call for aid for first-stage research, the Deshpande Center has used $706,000 to fund eight teams that are working on budding innovative technologies. The projects reflect the philosophy of this center. For example, the only available treatment for mouth cancer today is the IV administration of a chemotherapeutic drug with strong side effects. A team supported by the Deshpande Center aims to develop an oral administration system to reduce side effects; administering such local treatment has greater efficacy in these tumors. Another is researching an intraocular lens for cataracts, which would also release the drug that today is administered over the following weeks via drops. A third group is researching treatments for joint injuries in order to avoid developing arthrosis, from which quite a few patients suffer ten to fifteen years after the traumatic event.

Moreover, Esther Dyson and Mike Moradi agree that **"good technology is not enough. There are startups that don't make it due to management mistakes."** For Kivel, **"the risk of failure is much greater in the healthcare industry than elsewhere**, because it is not just about giving consumers a good product: you need to deal with authorizations, reimbursements, continuous investment rounds, then introducing this drug in other countries, alliances needed... The plan cannot just include some stages: it needs to foresee them all."

Proposals to Lure Investment to Startups

What factors may turn the landscape around? According to Patrick Flochel, there is no doubt that "we all wish there were more collaboration, big companies working together with startups, innovators, academia, patients... It is starting to happen, for example, more information is being exchanged, even data on what has not worked, in order to save money and to be more efficient."

There are non-profit organizations that are funding startups or academia, filling in the void left by the industry

Mike Moradi sees "reasons for hope. **There are non-profit organizations that are funding startups or academia, filling in the void left by the industry**. For example, the **Juvenile Diabetes Research Foundation** has an aid program to forge industry-academia alliances. It contributes one million dollars over two years. **The American Diabetes Association** endows the Pathway Initiative, which basically gives half a million dollars per year over five years to researchers working on new treatments. I think different players are making peace with what they believed would be a viable model one day, as they create new models."

According to Richard Kivel, **implementing a real, interdisciplinary culture in academia is essential**. "We have all been familiar with 'siloed' universities, where the chemistry department won't talk to the biology department, biologists won't talk to engineers, and none of them talk to business majors. This is changing, especially in the United States. William Haseltine, for one, is part of the Koch Institute, probably one of the big groups leading integrated medicine: it gathers physicists, molecular biologists, chemists... people from multiple fields working together. Therefore, **greater integration in universities is needed**, something I can't see happening in Asia, and only in a few places in Europe. **Integration will bring new technologies we had never seen in the silo-model."**

Another condition Kivel believes is essential is that "universities must have patent, license, and research result transfer departments that are efficient, effective, and operational. Most universities allocate scarce budgets to this end, so researchers have to beg for technical support to patent their findings, and even then it is considered an expense. Being more open to exploring intellectual property rights is not enough. They must become business development units actively seeking partners to

Universities must have patent, license, and research result transfer departments that are efficient, effective, and operational

market a product; people who see opportunities in the research undertaken in their universities, and people who know who to call at Pfizer, Lilly, or the local startup who just got funded, because they could be interested in licensing this technology or product, generating revenues, and feeding the system,"

Patients, a Key Player

Esther Dyson believes **involving patients is part of the near future**. "I would like to see education for the general public on how drugs work, medical processes, and the importance of therapeutic compliance, that is, finishing your treatment even if you feel better, to avoid a relapse. **People need to know more in order to manage their health better."**

Patrick Flochel believes **"we must put the patient at the center of everything we are doing**. This includes formally recognizing their ownership of their healthcare data, so that they can do with them as they see fit: give them to you—or not—, grant or deny access to third parties, waive it for research purposes… And of course, rewarding those who become actively involved in their health."

Education for the general public on how drugs work, medical processes. People need to know more in order to manage their health better.

Dyson gave several examples of initiatives that prioritize knowledge on health and disease that may be extracted from personal data. "In **23andMe**, you pay for the genetic analysis, but you may also waive your data to be added to a data base. When comparing them to other people's data, very valuable information is obtained."

In fact, 90% of the 150,000 patients 23andMe had in July 2012 take part in online research, which is generating **a phenomenon known as "crowdsourced science**," similar to "crowdfunding," where **individual contributions that would not be very useful by themselves, multiply their capacity to add value exponentially**—in this case, knowledge—**when adding tens of thousands of people.**

These data have been very useful for 23andMe to, among other findings, identify five new relevant genetic associations of hypothyroidism, a pathology affecting 5% of the population[1]; twenty genetic factors having an impact on short-sightedness[2] —which reveals the genetic complexity of this visual alteration—; and at least three genetic regions related to breast cancer, which, surprisingly, are also related to the size of the breast,

[1] Eriksson N, Tung JY, Kiefer AK, Hinds DA, Francke U, et al. (2012) Novel Associations for Hypothyroidism Include Known Autoimmune Risk Loci. PLoS ONE 7(4): e34442.

[2] Kiefer AK, Tung JY, Do CB, Hinds DA, Mountain JL, et al. (2013) Genome-Wide Analysis Points to Roles for Extracellular Matrix Remodeling, the Visual Cycle, and Neuronal Development in Myopia. PLoS Genet 9(2): e1003299.

which provides clues for a better understanding of the subtle interactions between morphology and risk of suffering the disease[3]. Also, interview-based research has discovered that, contrary to expectations, there are minimal negative reactions to information on cancer predisposition by the individuals affected[4].

At the end of 2012, the company received over half a million dollars from US National Healthcare Institutes to promote three projects: the first will research the genetics of allergies; the second will assess the accuracy of new sequencing technologies in clinical applications, and the third will develop tools to make a better use of genetic information saved by 23andMe to accelerate research in this field.

PatientsLikeMe sells anonymized data to the pharmaceutical industry and research institutions, who thereby gain extensive knowledge on patients' needs and the evolution of diseases in real life

Another initiative leveraged on the willingness of patients to share their data—an example shared by Esther Dyson—is **PatientsLikeMe**. Founded in 2004, today there are almost 200,000 patients representing over 1,500 diseases. In PatientsLikeMe you can input data on a daily basis on your pathology, symptoms, treatment (and progress when applicable), hospital admissions, changes in parameters measuring the progression or regression of the disease, weight, and perception of factors having an impact on their quality of life. The platform turns data into statistics and shows back graphs, where you can identify patterns and compare them against other patients' patterns, giving you an idea of how to improve your health.

This flow of data generates very valuable, real information, which, to-date, has translated into 25 publications in peer-reviewed journals. Also, it enables testing and dismissing a hypothesis in record time without recruiting patients for clinical trials. For example, a 2008 study on a small sample of patients suggested that lithium carbonate—a drug for major depression—could slow down the progress of amyotrophic lateral sclerosis, a disease that is incurable today. Hundreds of people on PatientsLikeMe started to take it, and in nine months, a study was built based on data from 348 patients that dismissed the positive effect attributed to this substance. Even though the team of researchers clarified that the

[3] Eriksson N, Benton GM, Do CB, Kiefer AK, Mountain JL, Hinds DA, Francke U, Tung JY., Genetic variants associated with breast size also influence breast cancer risk. BMC Med Genet. 2012 Jun 30;13:53.

[4] Francke et al. (2013) Dealing with the unexpected: consumer responses to direct-access BRCA mutation testing. *PeerJ* 1:e8

analysis of data contributed by patients does not substitute randomized, double-blind studies in advanced clinical research, this may be a useful tool in some cases.

The business model of PatientsLikeMe excludes advertisements, but it sells anonymized data to the pharmaceutical industry and research institutions, who thereby gain extensive knowledge on patients' needs and the evolution of diseases in real life. Among the company partners benefitting from this information are Abbott Labs, Biogen Idec, Boehringer Ingelheim, Merck, or Novartis.

In early 2013, the **Robert Wood Johnson Foundation** granted PatientsLikeMe a $1.9 million subsidy to develop the first open, patient-centered research platform to measure healthcare results. This new information will provide a very clear picture of patient experience to traditional studies on this field, and it will measure the quality of life in terms that are most important for patients.

Innovation Inhibitors and Accelerators

Attendants to the XIX Future Trends Forum discussed the main innovation accelerators and inhibitors in academia-industry relations, the role of startups, and the patent and licensing system.

Academy – Industry

Inhibitors

- The traditional structure of pharmaceutical companies needs to adapt in order to take on the role of collaborating with university laboratories, as opposed to cannibalizing them.
- Different cultures in both types of institution: this barrier is overcome, according to XIX FTF participants, by acknowledging, assuming, and respecting differences, particularly on the part of multinationals, which must be flexible with the way academia works.
- Culture, mainly understood as lack of initiative for detecting market opportunities to research and carrying out technological transfer efficiently. In this regard, researchers must be trained in entrepreneurship and business, and venture capital must be allowed to contribute their strategic operational vision.

Academy – Industry

Accelerators

- Identifying talent as it emerges in the breeding ground of universities. It must be encouraged, not changed.
- Online technology, which enables the constant Exchange between academia and the industry, and working around the clock with multiple geographic locations.

- The active involvement of the Administration, not only to fund research, but to demand that promising results obtained from research are taken past all the stages to a marketable product.
- Having operational systems to obtain high-quality patents that protect and provide a return on the results of research.

Startups

Inhibitors

- An excessive dependency on venture capital, which in the last few years has chosen advanced products instead of early research. Public funds and securitization are emerging as alternatives.

Startups

Accelerators

- R&D cuts in big pharma companies. This is a collateral effect, but the truth is that budget cuts in the industry open a market niche for startups, since there will be fewer players competing in multiple research niches.
- Open innovation, a collaboration system where startups made up of five to ten researchers very focused on developing a project receive aid from other structures—starting with, but not exclusively, the industry—that are more familiar with the marketing stage, to guarantee the project will come to fruition.
- From the perspective of capital investing in startups, the key accelerator is "the right people:" the researcher can expand horizons or find solutions not yet considered by the representatives of established knowledge.

- A favorable tax regime, in the form of tax deductions, for example, to invest in innovation.
- All people involved in the startup must own a stake in the company, since this exponentially increases their capacity to become involved and drive the project.

Patents

Inhibitors

- The so-called "patent trolls," that is, companies that sue others for allegedly violating their IP rights with the exclusive—and oftentimes successful—goal of reaching an agreement so that the legitimate owner avoids a costly, time-consuming lawsuit.
- Competition between those who profit from the patent and those who profit from its expiry, such as generic drug companies.

Chapter VI.
17 Impactful Proposals to Promote Innovation in Drug Development

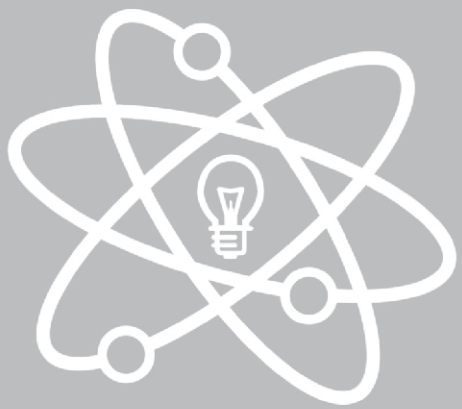
Reducing Costs in Stage 3 of Clinical Trials

Tomorrow's Business Models

New Markets: the Engaged Patient

Promoting Start-ups

Shortening Development Times




3

Reducing Costs in Stage 3 of Clinical Trials

1. Tapping into the Opportunities of Electronic Clinical Records.

Electronic Clinical Records (ECR) is the tool with the greatest potential to identify patients with the optimal profile to join a clinical trial, or those who most need the drug that is being tested. The wealth of data gathered by the electronic clinical records—from the evolution of symptoms to lab results and image tests—and the convenience of crossing data and creating profiles with them **makes this tool revolutionary**.

Moreover, the ECR is not only useful for doing a search when a specific need arises: you can have preset parameters, so that when a patient enters a hospital, an automatic alert goes off if requirements are met for joining a trial underway.

Biomarkers predict a patient's response to a drug, understand the molecular base of multiple diseases, develop fast and non-invasive assessment techniques for treatments

2. Relying More—and Better—on Biomarkers.

Biomarkers are becoming one of the pillars of the 21st century Medicine. They predict a patient's response to a drug, understand the molecular base of multiple diseases, develop fast and non-invasive assessment techniques for treatments, obtain diagnosis via analytical tests before severe damage occurs—such as cancer or acute renal failure—, enable doing the risk profile of potential diseases based on the genetics of an individual, and open the door to more effective early prevention strategies. The number of diseases for which biomarkers are discovered is continuously growing. Pandemics resulting from improved life expectancy, such as Alzheimer's or Parkinson's, are on the horizon of research: the role of biomarkers is especially important for early diagnosis purposes. The deterioration behind the onset of these diseases takes place much earlier than the first symptoms—when they are already irreversible.

Biomarkers are showing signs of becoming extremely useful for clinical trials. First, to determine which patients will benefit the most from drugs being tested, so that they are not unnecessarily subject to the toxicity of drugs without their clinical use. Second, to assess treatment results as the trial unfolds and adapt its design, progressively focusing on the substances that show the greatest therapeutic success. This

way, molecules entering stage 3 would be better selected, and therefore, fewer but better selected patients would be needed, thereby considerably reducing the cost of the trial.

For biomarkers to become the standard in clinical trials; genomic, biochemical, and biomolecular analysis technology must continue to develop in order to truly become cost-effective; and be added to the portfolio of services of analysis laboratories of tertiary hospitals, instead of being restricted, as is the case today, to a few, super-specialized centers.

Current developments also support measuring your lung capacity with your cell phone as if it were a spirometer, assessing sleep alterations

3. Promoting Remote Clinical Trials.

Rising at-home care increases the number of candidates for clinical trials physically located outside the hospital. Also, attendants to the XIX FTF agree that not having to depend on whether the patient is hospitalized, or must travel regularly to a healthcare center for the purpose of the trial, amounts to quite some savings. Current technology enables uploading secure, confidential data to web platforms. There is a considerable impact brought about by this approach to minimize the burden on the participants and the cost structure.

One possible limitation of this system is the participants' persistence in including their data at the right time. Attendants to the XIX FTF believe it is not realistic to question the reliability of trials based on this reason. On the one hand, an individual's interest in improving his/her own health and effectively fighting against the disease is a very powerful stimulus for being actively involved. On the other hand, there are more apps for smart phones—backed by healthcare authorities—that collect data and upload them directly to the corresponding server. Measuring blood pressure and blood sugar levels or having an electrocardiogram done is already possible today with these devices. Current developments also support measuring your lung capacity with your cell phone as if it were a spirometer, assessing sleep alterations, or detecting substances in urine with a cell phone camera. And the number of applications continues to grow.

A remaining challenge is collecting blood samples at home without cold conservation to make it easier to send them to the healthcare center for biochemical analysis. The research underway is expected to overcome this barrier in the future —thus closing the cycle. Furthermore, there are groups of pathologies that do not require this type of analysis, where relevant information comes from the evolution of symptomatology

Ir is necessary to have an electronic clinical record than can be accessed by stakeholders from multiple areas

and other circumstances, such as troubles or side effects, shared by the patient. This is the case for example, in anxiety, depression, pain...

4. Standardizing and Integrating Data

This is necessary in order to have an electronic clinical record than can be accessed by stakeholders from multiple areas, as well as to integrate clinical data with the data generated in clinical trials, so that sources give feedback to each other.

Tomorrow's Business Models

5. Introducing the Single-Drug Company Model.

One problem faced by the pharmaceutical industry for years now **is the constant slowdown in R&D productivity: the magnitude of funds** allocated to this area—making it the world's innovation engine—**does not correspond in due proportion with the results attained.**

To efficiently transfer knowledge to the market, the experts taking part in the XIX Future Trends Forum propose **creating "single-drug companies,"** that is, **made up of a core of researchers**—three to ten people—**directly involved in clinical trials and managing the development of one single drug.**

Create single-drug companies that is, made up of a core of researchers—three to ten people—directly involved in clinical trials and managing the development of one single drug.

The main differences with a multinational are: the bare minimal structure (and the subsequent reduction in costs); the stakeholders in the project own the company—which gives them an incentive, they are not employees of a big company—; the possibility of accessing alternative sources of funding; and work focused on the clinical need to be met, without the pressure of making a blockbuster product to balance the P&L of a multinational company.

6. Choosing Alternative Sources of Funding: Seed Capital, Patients' Associations, Securitization…

Single-drug companies basically start with one idea or discovery with the potential of meeting an existing clinical need, or doing so for a fraction of the cost, with greater efficacy or improved quality of life for the patient.

This approach makes them suitable for both small and big drugs, measured in terms of the population targeted, thus opening access to new sources of funding, for example, different types of seed capital: a business angel but also patients' associations that are increasingly sensitive to research needs, and particularly active in organizing events to raise funds. The contribution by stakeholders will basically be of a financial nature, but—especially with rare diseases—it may also be a contribution in kind: to begin with, they will make it easier to gather people to participate in clinical trials; they may even contribute with professional skills, if there are specialists in toxicology or chemistry…

Crowd-funding may also play a role in promoting this type of company, which may also earn revenues through securitization. In this case, since the

company corresponds to the drug to be developed, this asset has the potential to generate royalties and it is a candidate for securitization that provides a source of income other than seed capital.

7. Evolutive Capitalization and Flexible Sizing

An advantage of single-drug companies is that their incorporation and capitalization have flexible timings and conditions, because they depend on their assets, and assets are judged by investors. Depending on the case, the main asset may be a compound discovered by academia, a therapeutic target, a group of particularly relevant researchers who, because of their talent, will appeal to markets; in these cases, the company would incorporate very quickly. In other cases, development will be fed by subsidies until it gets to stage 2 of clinical trials. Then, it will be formally incorporated and open to other sources of funding.

An advantage of single-drug companies is that their incorporation and capitalization have flexible timings and conditions

Likewise, the company's structure and funding only grows as research reaches certain stages to deserve such funds. This dynamic diversifies risk considerably. It is an incentive for successive achievements and minimizes the impact on researchers and investors of projects that end up coming to nothing.

8. Multiplying the Range of Products while Reducing the Risk.

The multinational pharmaceutical industry is a natural candidate to invest in single-drug companies with projects or promising initial results; or maybe, products in stage 2 of clinical trials with a good chance of being approved.

Since many one-drug companies will spin off from academia or startups, multinational companies may find in them thriving breeding grounds for research, precisely in a context where their own initiative is curtailed by limited corporate budgets for R&D. If a big company is interested in, let's say, neurology, it will probably find a broad market to choose from. It will decide to participate in the funding of selected companies when it sees fit from a strategic perspective, without the uncertainty of developing it from zero.

New Markets: the Engaged Patient

Lack of therapeutic compliance in Spain affects roughly 50% of chronic patients and 20% of acute patients

9. Aligning the Theoretical and Real Markets by Encouraging Therapeutic Compliance

Lack of therapeutic compliance in Spain—that is, not following the pharmacological treatment as prescribed by the doctor—**affects roughly 50% of chronic patients and 20% of acute patients**. Some studies suggest this problem could account for up to a third of hospitalizations, especially given the progressively aging population[1]. Not knowing how important it is to not stop your treatment even when symptoms have improved, forgetfulness, carelessness, adverse effects or the fear of suffering them are the most common reasons for lack of therapeutic compliance.

According to XIX FTF attendants, the pharmaceutical industry may make use of a field where new technologies make it easier to contact patients to remind them the importance of finishing their therapy, send a reminder when they have to take their meds, digitally monitor if they have actually taken them—even with a sensor attached to the drug…

Improvement in this regard has a very positive impact on the population's health, it avoids the cost of treating relapses—which oftentimes require hospitalizations—and has a positive impact on the turnover of pharmaceutical companies by aligning the theoretical and real markets.

10. Using the Stream of Data Generated by Patients for New Lines of Research.

With 23andMe, PatientsLikeMe, and others, participants may open up their personal data to others, generating a flow of data of great potential value, something that used to take a lot of effort and time to achieve. 23andMe links the genomic analysis to several features, including diseases and treatments. This opens the door to identifying what drugs have greater efficacy—or not—in what genetic profiles, which in turn, creates a

[1] Several Authors, Consensus Document. A multidisciplinary approach to the issue of therapeutic compliance in chronic diseases: situation as is and future prospects. 2012.

field of research for developing drugs suitable for those who are not really benefiting from current treatments.

One challenge is to link data to diseases as specifically as possible. On a different level, this is the case with projects like Collaborative Oncological Gene-Environment Study—financed by the VII Framework Program of the European Union—where 74 new genetic alterations linked to breast, ovarian, and prostate cancer have been discovered thanks to data from one hundred thousand cancer patients and one hundred thousand healthy people. These genome "errors" are barely relevant by themselves, but they have a cumulative effect on the predisposition to the disease[2].

Thanks to data contributed by patients themselves we know how medicines work in real life in much more detail

Likewise, thanks to data contributed by patients themselves we know how medicines work in real life in much more detail. Current systems for detecting side effects, discomfort, or interactions are limited by the fact that they depend on the doctor being notified, who must receive information from the patient, who could omit it for a number of reasons (not having an appointment scheduled, forgetfulness, it is a mild reaction...). This task is made easier by communities of patients, who provide drug developers with first-hand, real-time information to continuously improve the product, as well as aspects of the quality of life or the convenience of the therapeutic regime.

11. Creating Additional Markets through New Channels to Dialogue with Patients.

Ubiquitous mobile devices are changing how patients interact with their own health. In April of 2012, one could access over 13,600 healthcare and fitness apps from Apple's AppStore, including: cardiovascular health, diet, therapeutic compliance, sleep monitoring, quitting smoking habits, education about health... At the same time, devices that record vital signs (pulse, heart rate, the use of asthma inhalers, measuring glucose...) have been developed and can transfer data to these applications and upload them to the Internet.

This new generation of patients and healthy people engaged with their own health will share their information without blinking, which provides a huge amount of data, and at the same time, opens new channels of dialogue between patients and the pharmaceutical industry.

[2] Nature Genetics, Focus issue: April 2013, Volume 45, No 4

Drug developing companies have an opportunity to become leaders in this field, given their credibility and scientific reliability

On the one hand, the pharmaceutical industry is expected to act beyond therapeutics in the healthcare system, as well as in prevention. On the other hand, there are no specific mechanisms today to approve or assess healthcare apps. However, the first studies show that, depending on the areas, only one fourth base their information on the best scientific evidence, and just as many have wrong data[3]. Drug developing companies have an opportunity to become leaders in this field, given their credibility and scientific reliability. Closing the cycle from prevention to treatment grants access to a new market: devices and applications.

On the other hand, apps generate relevant information for the industry. For example, some apps that record the use of asthma inhalers use geolocation technologies to find out what environmental factors and periods of time are associated to a greater prevalence of asthma attacks, thus adjusting treatments.

[3] van Mechelen DM, van Mechelen W, Verhagen EA.Sports injury prevention in your pocket?! Prevention apps assessed against the available scientific evidence: a review. Br J Sports Med. 2013 Mar 19

Promoting Startups

12. Creating a Culture that Values Risk

It is necessary to find ways to stimulate startups in life sciences, by driving a change that encourages taking on the risk of trying something new. According to attendants to the XIX FTF, this process will take years in some countries, because their initial positions are unequal.

It is necessary to find ways to stimulate startups in life sciences, by driving a change that encourages taking on the risk of trying something new

According to the OECD report, "Entrepreneurship at a Glance 2012," from the first quarter of 2006 to the second quarter of 2011, the number of new companies in Spain shrank by 43%, compared to 3% in the United States and Finland, 16% in Denmark, or 15% in Germany. In the United Kingdom, however, this number grew by 8%, and 100% in France.

Fear of failure is a strong cultural idiosyncrasy. According to "Global Entrepreneurship Monitor," even though 65% of Spaniards believe starting up a business is a good way of driving your career, only 14% believe there are good opportunities to do so. Out of the latter, 39% acknowledge that fear of failure would hold them back.

In Belgium, Brazil, or Mexico, 43% believe opportunities abound; in Denmark, Switzerland, Australia, and the Netherlands, it's between 45% and 50%, and above 60% in countries such as Finland, Norway, and Sweden.

Attendants to the XIX FTF highlight that failed attempts are part of a businessperson's natural learning process, they must be valued positively both from a personal and social perspective.

13. Supporting Startups with Suitable Legislation and Fiscal Regime.

In a list of 185 countries, **the World Bank ranks Spain number 136 in how easy it is to start up a company**, that is, **Spain is among the 50 countries with the most restrictive conditions**[4] . It is only surpassed by countries like China, India, the Czech Republic, Greece, and Malta. Among the "OECD High Income" countries, Spain is number 29 out of 31.

[4] The World Bank. Doing Business. Measuring Business Regulations, June 2012.

Where you can start up a company in one or two days in Australia and New Zealand, it takes almost thirty in Spain. OECD countries usually require four to six steps to start up a company, which become ten in Greece and Spain.

The last report on Spain by the "Global Entrepreneurship Monitor 2011" shows an entrepreneurship rate of 5.8% among Spaniards between 18-64 years old. The figure is higher than in 2010, but the authors of the report consider the increase is partly explained by necessity and unemployment.

In the XIX FTF work sessions, the value of tax deductions was highlighted, especially in an environment where direct aid to research is dwindling because of public budget cuts.

Tax incentives for R&D are clearly justified in any country's global economic policy

Tax incentives for R&D are clearly justified in any country's global economic policy, according to the OECD[5] . On the one side, economic growth and competitiveness are clearly linked to intensive R&D. On the other side, research is a risky activity where, correspondingly, one may find additional difficulties to access financing, so it makes sense to compensate this inconvenience with fiscal advantages. Finally, a favorable tax environment attracts foreign investment to innovation.

XIX FTF participants mentioned as an example the unwavering approach of Canada or France in this regard. Canada offers a 35% deduction to small companies for the first CAD $3 million invested in R&D, and a 20% deduction onwards. For big companies, the deduction is 20%. France offers a 30% deduction for the first €100 million and 5% afterwards. For companies profiting from this deduction for the first time, the rate is 50% the first year and 40% the second year. The State ceases to receive CAD $3.2 billion in Canada (2008) and €5.6 billion in France (2009).

[5] OECD, R&D Tax Incentives: Rationale, Design, Evaluation. November 2010.

14. Looking for New Types of Alliances with the Pharmaceutical Industry.

Venture capital is proving to be reluctant to invest in pharma and biotechnology, an industry where the level of uncertainty is high and the average profitability between 2006 and 2010 barely reached one third of information technologies[6]. In the United States, first rounds of funding decreased by 19% in 2011: only 98 out of 446 agreements that year—for a total of $4.7 billion—had a startup at the end of the line.

Venture capital is proving to be reluctant to invest in pharma and biotechnology, an industry where the level of uncertainty is high and the average profitability between 2006 and 2010 barely reached one third of information technologies

Some big pharmaceutical companies are trying to fill that void, although their contribution is limited—at 15% of venture capital's stake. Some noteworthy examples are the funds created by MSD in September of 2011 with $250 million each: the Global Health Innovation Fund and the Merck Research Venture Fund. In March of 2012, GSK and Johnson & Johnson joined Index Venture to create a $200 million fund to promote budding biotechnology companies.

Finding new alliances will take pressure from shareholders off the pharmaceutical industry; this is necessary so as to diversify risk.

The market has already witnessed some examples of such relationships.[7] Forma has assigned Genentech the rights on its new cancer drug programs. The startup will receive an initial capital injection, and additional payments will be subject to the success of subsequent project stages. The agreement grants Genentech the right to directly acquire the resulting compound, instead of a marketing license. This way, the startup secures venture capital without going public or being acquired by another company; working towards its sustained growth.

Adimab and Nimbus Discovery have chosen to sell access to their technological platform to discover new antibodies, instead of embarking on developing the corresponding drugs.

Quantice Pharmaceutical has licensed its platform to Celgene for three and a half years to analyze genetic variants in tumors, in exchange for

[6] MoneyTree Report from PwC and the National Venture Capital Association, based on data provided by Thomson Reuters.

[7] PricewaterhouseCoopers, Biotech. What's next for the business of big molecules?, 2012.

$45 million. The agreement grants Celgene a stake in the company and an exclusive buy-option on Quanticel in the future.

The alliance between Ward Drive Bio—specializing on plant and animal genome analysis to develop new products in the future—and Sanofi, gives Sanofi a non-exclusive buy-option on the company. If Sanofi does not use this option, Ward Drive Bio will keep the rights on many of the active principles it develops. But if it reaches certain targets, it may even force Sanofi to acquire it at a previously agreed upon price.

15. Reinforcing Relations with Academic Research

This is a line of work where big multinationals are coming on strong: it is about **"going where science is being made."** Johnson & Johnson has recently announced four research centers that will be launched in big scientific communities in Boston, California, London, and China. Merck has established the California Institute for Biomedical Research in San Diego to carry out initial-stage research. Bayer's alliance with the University of California in San Francisco also pursues the connection between basic research and drug development. Pfizer's translational research network includes twenty universities and university hospitals in the United States alone. One more example: Open Innovation Drug Discovery: through this platform, Eli Lilly is collaborating with external scientists—mainly from academic institutions—to identify new compounds with a therapeutic use. In the first 18 months, it has attracted no less than sixty European institutions.

Shortening Development Times

16. Breaking the Clinical Trial Paradigm.

The participants of the XIX Future Trends Forum advocate doing away with the classic paradigm of dividing clinical trials into preclinical studies, stage 1, stage 2, stage 3, and stage 4. The problem with this structure is that it focuses on stage 3—trials with thousands of patients, that are the key to drug approval—towards the end, and because of this, the rest of the pieces in the puzzle must conform, so to speak, to this goal.
Experts gathered in the work sessions of the Bankinter Foundation of Innovation propose approaching the trial as a continuum, where design is adapted to results that are subsequently obtained.

17. Unifying Criteria among Authorization-Granting Agencies

Unifying the criteria is necessary so that the actual process to finally launch the drug in each market does not extend indefinitely

A problem faced by pharmaceutical companies is that the actual life span of their patents is shortened by negotiations on price and reimbursement conditions with healthcare authorities in each country once they have been authorized by the European Medicines Agency.

This process is time consuming, and also a sort of second authorization. Where the EMA bases its decision on quality, safety, and efficacy of the compound, national agencies—such as the British National Institute for Health and Clinical Excellence (NICE)—value something else: cost-efficacy. If an approved drug were not publicly funded, this would tremendously hinder a return on investment of the development. Other administrations demand additional studies in their specific countries to approve the price.

Unifying the criteria is necessary so that the actual process to finally launch the drug in each market does not extend indefinitely. Calculating a return on investment is difficult without knowing specific deadlines and terms—and this may jeopardize innovative research.

Chapter VII. The Future of the Value Chain in Drug Discover: Scenarios

Citizens

Pharma Industry

Academia

Patients

Regulators and Society

Political Decision Making


F CELL
THERAPIES

If the high-impact proposals formulated at the XIX Future Trends Forum to ensure innovative drugs are pumped into markets were to be implemented, what would the future look like? Experts gathered at the XIX Future Trends Forum imagined a scenario where suggested improvements have been implemented across the board. Then, they analyzed the impact on research, drug approval, access to new drugs, public healthcare system budgets, the attitude of the citizens, the funding systems, and the structure of the pharma industry... The goal: to outline the incentives and lines of action that may contribute to this future becoming a reality. The following is a summary of the ideas-strengths that came up in the discussion.

Citizens

Biomarkers are the doorway to predictive medicine—what pathologies are more likely to be developed based on the genetic profile—**and personalized medicine**, since it may be known, given one specific disease and patient, what drugs are effective and which ones are not, despite being broadly indicated for that pathology (specifically in cancer cases).

What implications will this scenario have for patients? According to XIX Future Trends Forum attendants, the implications are broad and different in nature:

People will decide if they want to know their genetic information and how to use it to adopt a healthy lifestyle and habits

- **More information, more decision-making capacity**. People will decide if they want to know their genetic information and how to use it to adopt a healthy lifestyle and habits—the kind that may have an impact on the diseases they are predisposed to—and to decide whether to go to the doctor or not, undergo certain treatment or not, take certain preventive measures or not (getting a mastectomy when there is a risk of cancer becoming worse, for example).
- **Direct intervention in drug development.** Patients with more information will become more involved and look for solutions for their diseases. Biomarkers reveal promising therapeutic targets for which patients' associations may raise funds and create single-drug companies, thereby becoming an active player in research and marketing of compounds in some cases.
- More information, more responsibility. Greater knowledge of the genetic and molecular base of diseases and their risk factors will proba-

bly open up the social debate on one's personal responsibility for one's own health. As certain disorders are considered avoidable by adopting healthy habits in due time—weight and blood pressure control by means of a suitable diet—will society still be willing to share the burden of treating certain disorders?

- Data overload. Another area of focus is the right not to know, the right to avoid the consequences of the excess of information, especially in the case of elderly people or individuals with a low level of education who feel unprepared to navigate multiple scenarios and make complex decisions. These people would typically reply: "What would you do if you were in my shoes, doctor?"

Biomarkers will reduce the futility curve, since the drug will be effectively administered to the patient who will truly profit from it at the most appropriate time

- New challenges in terms of privacy. Data contributed by patients via online services or specific communities are extremely valuable for research purposes, but they entail confidentiality and security issues that the legal framework must properly address. Moreover, there are two types of risk: on the one side, breach of confidentiality; on the other, an unsecure system that could put people off from sharing information that could provide a lot of potential for them and others in similar situations. In the case of clinical trials with minors involving genetic analysis, there is the question of what control the patient will have over data assigned by his/her parents when he/she becomes of age.
- Social participation in the debate about resource allocation. Medicine—particularly genomic medicine—promises spectacular progress and ever-more precise drugs, but it may also be more expensive. Biomarkers will reduce the futility curve, since the drug will be effectively administered to the patient who will truly profit from it at the most appropriate time; and hence, avoid administering expensive treatments to people who will not obtain therapeutic results. In this context, the profit of each euro spent on health care will be maximized. But the success of medicine is translated into greater longevity, and in the medium to long term, into a healthcare system that uses up more resources. A public discussion on priorities seems unavoidable in the near future: will the healthcare system be more expensive or cheaper? Should budgets prioritize prevention or healing; chronic or acute diseases; high-resolution centers or at-home care; transplants or integral care for the elderly….; funding basically all drugs or just a few to be able to reach a larger population?

Pharmaceutical Industry

The future will bring new sources of funding and business models in the form of new types of alliances, and improvements on the costs and time frames of drug development, including clinical trials. What implications will this scenario have for the pharmaceutical industry? These are the implications identified by attendants to the XIX Future Trends Forum.

- Information provided by **biomarkers will pave the way to the discovery of high-quality drugs in early stages of development**. Molecules with the potential of becoming a drug will be identified earlier, and the process will be faster and cheaper.

Biomarkers will pave the way to the discovery of high-quality drugs in early stages of development

- The social standing of the pharmaceutical industry will improve as drugs with greater efficacy and fewer side effects are created.
- Biomarker-based treatments adjust to the genetic profile of patients and diseases (tumors from the same organ or tissue that in reality are different, depending on the DNA region involved). They are better because they are more specific, that is, less universal. A smaller target population will probably affect sales revenues; in other words, **the industry**—according to the XIX FTF experts—**will have a tighter profit margin per product**. It remains unsettled whether smaller margins will be offset—and to what extent—by fewer development costs.
- Changes to the current picture of pharmaceutical multinationals due to this phenomenon cannot be ruled out. **Some companies may be headed for a thorough overhaul.**

Academia

New business models: single-drug companies, active alliances with the industry, startup creation…

- **New business models (single-drug companies, active alliances with the industry** under the umbrella of open innovation, **startup creation** based on spinoffs from universities and clinics…) offer a path towards the final development of a product based on ideas and research that would have been cut short in the past.
- More opportunities and practical results of academic work through these agreements will increase the appeal of research and lure more talent to their institutions.
- A pharmaceutical industry more engaged in academia may have a positive impact on issues that universities have traditionally neglected, such as putting together multi-disciplinary teams and creating incentives linked to results.
- If the pharmaceutical industry reduces corporate research and development budgets and looks for partners in other centers with early stage compounds, therapeutic targets or promising hypotheses, it will encourage a sense of competition and benchmarking in academic research.
- In the eventual overhaul of the pharmaceutical industry, including downsizing or winding down some companies, part of the staff could feed the ranks of academia, either thanks to their research experience, their management expertise, or both.

Patients

- **Patients' associations are increasingly structured—and better so**. That is how they have increased their influence on society and their ability to dialogue with healthcare administrations.
- Also, they are a highly valuable source of aggregate data to generate knowledge and to develop drugs.
- Now that **venture capital is unwilling to invest in the pharmaceutical industry, and the industry tends to jump in more advanced stages of product development, patients' associations may reveal themselves as a player that is fully capable of co-funding early-stage research projects.** In this regard, they are a player of the utmost interest for startups too.
- Because of the abovementioned reason, these associations must be professionalized, or at least need to receive suitable advice so as to value the strength of new scientific approaches, and duly manage their participation in funding. As pointed out by XIX Future Trends Forum participants, the credibility of those who are particularly sensitive to the drama of disease could be abused. The capital injection, linked to the achievement of successive milestones, seems to be the most suitable and transparent process, offering greater security to the parties.

Patients' associations are increasingly structured—and better so

Regulators and Society

- If the scenario proposed by the participants at the XIX Future Trends Forum becomes a reality, the market would have more drugs and would meet more clinical needs thanks to new therapies. Above all, the market would have greater transparency, because it would be known what percentage of patients will respond favorably to drugs, or the percentage that will develop drug toxicity —once again, thanks to biomarkers. Transparency is a key factor in the degree of public satisfaction with healthcare spending, especially when the expenditure increases.

Health care accounting for an increasingly larger percentage of every country's gross domestic product

- **Opening the market of rare diseases.** The main reason why rare diseases—whose prevalence is below five cases per ten thousand inhabitants—**do not attract research is because the critical mass of patients makes them scarcely profitable as market niches.** XIX Future Trends Forum members see a horizon where regulatory authorities will validate clinical trials with fewer patients for these pathologies.
  The Administrations require a greater number of subjects in stage 3 trials—this, along with extended time frames, is the main reason why clinical trials are increasingly expensive—the greater the target population is. The reason is that they will claim a much more thorough safety and efficacy evaluation for drugs that treat a highly prevalent symptom or condition—that is, suffered by many people.
  In the case of rare diseases, it is logical that these requirements should adapt to the number of patients . This would benefit both patients—who would obtain a research effort that is currently non-existent—and the industry, which would face costs that are more proportional in size.

- A true social dialogue on budget priorities. Basically all forecasts point towards **health care accounting for an increasingly larger percentage of every country's gross domestic product**. In a transparent market, an open, impartial debate could take place on the portfolio of healthcare services. Consensus would be reached on what drugs should be guaranteed for everyone based on their cost-efficacy, and what drugs should be privately funded. Regulators, patients, administrations, economists, scientist, and clinicians should participate in this debate.

- The economic profits of health should be more evident. There is a permanent discussion around the burden of the healthcare system on national and regional annual budgets, particularly in times of economic uncertainty. This is how bias creeps in, that each new technology is an additional expense.

The widespread standard in the XIX Future Trends Forum is to first think about the profits of clinical and technological progress, including its economic impact. So, for example, the vaccine against hepatitis B has prevented many kidney cancer cases, a disease that entails—aside from the evident cost in lives—hospitalizations and expensive oncological treatments.

On the other side, the more health, the greater productivity in the country, an aspect rarely mentioned explicitly when assessing the cost-efficacy of new treatments.

To first think about the profits of clinical and technological progress, including its economic impact

- At the same time, governments are asking for an additional effort from the pharmaceutical industry to contribute to a sustainable healthcare system, where they are to become healthcare players, focused on prevention. This discussion goes on along with approaching management inefficiencies in the healthcare system, in the hands of managers and clinicians.
- An environment must be created where information on failed clinical trials is shared. Today, those data remain unused because of the confidentiality terms imposed by sponsors when the expected results are not attained. However, they are a highly valuable source of knowledge to avoid duplications in research, which prove to be very costly in terms of funds, time, effort, and talent that could be used in other areas. Knowing what has not worked and why is almost as useful as knowing what has worked.

- The risk of genetic discrimination. Disease today is still largely considered to be random. The possibility of analyzing each person's genome and the progressive discovery of genetic regions involved—almost always multifactorially—in the onset of certain diseases sheds light on predispositions, which gives patients greater control on the evolution of their health, and the pharmaceutical industry obtains new pathways to drug development. But it also gives healthcare insurance companies a new way of classifying risk and adapting premiums or exclusions accordingly. The multidisciplinarity analysis undertaken by the XIX Future Trends Forum agrees that **the law must regulate on this matter, so that genetically-based discrimination is prohibited.**

- Real access to healthcare data. In no few legislations and in the culture of many healthcare centers, there is a predominant idea: healthcare data belong to the institution providing health care, not to the patient. It is key for the law to regulate the effective access by citizens to available information on their own health.

The law must regulate on this matter, so that genetically-based discrimination is prohibited.

- Sharing samples and data for research. Thousands of healthcare data and hundreds of biological samples subject to analysis are collected every day by hospitals. An adequate protocol on how to collect, classify, and file this information, so that it may be accessed from remote systems—as remote as one wants them to be—will make them usable in several areas.
  First, healthcare services will know precisely the use given to drugs. Second, they have huge research potential for startups, who obtain high-quality epidemiological data for their studies from anonymized data and biological samples.

- **Guaranteeing a tax system that spurs cooperation among international teams**. The law must find solutions for projects that are based in one country but attract researchers from other countries. When the retribution is in cash, the tax regulation should foresee how to avoid double taxation and tax cuts—if there are any—on research, but if it takes the form of options on shares, this is not always appropriately considered.

- **Integration of policies**. Innovation, drug authorization, tax incentives, and training are issues that fundamentally influence how science is done in a given country. However, these four areas normally depend

on different government departments and there are many examples—in Spain and beyond—of the lack of coordination among them. Qualified experience from XIX Future Trends Forum participants do not hesitate in pointing out **coordinated policies as a decisive stimulus or hindrance**. Such alignment must not only be horizontal, but vertical, so that federal and state governments, or state and regional governments, develop mechanisms to steer projects through the multiple proceedings.

Coordinated policies as a decisive stimulus or hindrance

- Public-private cooperation. The legal framework creates rigidities to public research bodies that make it difficult—and sometimes completely exclude the option—to ally with financial backers or private research institutions. There is a need to establish a legal framework on how to use data or samples available in public centers for public-private projects, and what is the implication—and how it is articulated—and dedication of researchers at these centers in these types of projects.

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