An Intercultural Experiment to Build Life Science Innovation in Korea

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Abstract

The establishment of Institut Pasteur Korea (IP-K) has been an intercultural experiment, which transplanted a French research organization with many foreign researchers into Korea to grow a new institution as a long-term collaboration. The Mission of the newly founded institute has been to develop more effective ways of generating value with basic life science research in the face of a world-wide Pharma crisis. The challenges have been i.) to invent new technologies and approaches in drug discovery, ii.) to convince the Korean stakeholders of their inherent value, iii.) to induce Pharma industry to adopt the new technologies and iv.) to create a context in the Korean R&D landscape where the new institute could contribute tangible benefits. If Institut Pasteur Korea has succeeded in all counts, then due to a somewhat skewed and unlikely set of cultural complementarities between Korea and France. The abstract and conceptual French approach was matched by Korean pragmatism, linearity and relentless improvement towards the defined development goal. IP-K has become an example for innovation made in Korea, which is now re-imported into Europe. As the project could arguably not have succeeded in either partner county alone, it highlights the benefits of long-term, in depth international collaborations.

KEYWORDS: life science, pharmaceuticals, translational research, biotechnology

1. INTRODUCTION

Korea has managed to develop itself in a very pragmatic fashion into a highly educated and industrialized nation. It has the ability to compete in all major industries and now surpasses many international industry leaders. Korea has arrived at a stage of development where future growth and living standards simply cannot be derived from benchmarking improvements. The current challenge is

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the transition from improvement to innovation.

Decision makers understand that the collective skill-set of quickly emulating and improving is a model that differs from innovation. Innovation cannot be copied; however, many emerging economies have successfully evolved their models from what often started as ruthless replication. Where does Korea stand in this respect? Are we about to witness the burgeoning of innovation driven industry sectors or is the penchant for improvement more deeply woven into Korean culture? Taking a close look at the crisis-ridden pharmaceutical industry may prove a reliable indicator of future changes. In this sector, innovation and improvement co-exist in a clearly delineated fashion, and the ability to innovate draws heavily on a prolific and creative academic knowledge base. It is here that Korea has staked its hope for future growth; subsequently, it has invited the Institut Pasteur for a long-term, international collaboration project in Korea to develop new ways towards innovative therapies. The establishment and operation of the Institut Pasteur Korea thus addresses two intriguing, intersecting questions: Is it possible to develop new technologies and approaches to re-start the innovation engine in the pharmaceutical industry, and of all countries, can that be done in Korea?

1.1. Making a case for Future Pharmaceuticals Innovation in Korea

What is innovation and what affects its attainability? Innovation is not invention. Inventions are generated by scientists in laboratories. Innovation is an invention that is accepted, adopted, and fully implemented by markets and society. Yet the term innovation is too often used incorrectly. The inflationary use comes along with a highly positive connotation in market driven societies. Why is innovation so desirable? The examples we are exposed to on a daily level are innovative consumer success stories that have created or opened large markets. Innovation is an extension of our appreciation of creativity, and is a concept that goes along well with our non-hierarchical and highly dynamic societal organization. Extending from this tangible and denotative understanding of innovation is a huge edifice of PR and ideology. Reference to innovation is a marketing tool, and policy makers like to draw on the opaque idea of innovation as an apolitical fix for social problems. There is also a very clear geographic association with innovation. After ‘Apple versus Samsung’, we have all learnt that California has it, while Korea wants it. To understand whether Korea may have a cultural liability in getting there it is important to remember that in almost all cases innovation is the result of a complex interplay between individuals and society. This interplay regulates innovation on two levels: i) the inventor who has to think independently and transcend established structures, and ii) on the level of group values in a society, in which established forces have to accept an innovative system potentially causing their replacement. This latter aspect is very important, as genuine innovation is not entering into a market or society as a neutral addition, but usually replaces existing products, habits, or structures. The drive for innovation is an intrinsically aggressive strategy that creates interlinked obstacles to innovation; on one hand it is a challenge for individuals to master the creative invention leg of the innovation process, while on the other hand there is a strong incentive on behalf of the establishment against the acceptance and implementation of such inventions. Thus, the more entrenched power structures within societies become, the more they will clamp

down on innovation. Subsequently, Confucian societies should impede innovation on both levels as they have hierarchal establishment structures and education systems that suppress the creative potential of individuals. Looked at within a purely cultural context then, the innovative potential of Confucian Korea should be disappointingly low.

If such cultural obstacles existed, they have not posed a problem to Korea's economic rise so far. Genuine innovation is a rare thing, and upon a closer analysis, many cases of recent innovation would be more correctly described as improvements. This is particularly true for the pharmaceutical sector. While we are hailing innovation, we ignore that economically improvement may be a more beneficial alternative that contributes more to the GDP than innovation. Improvement is continuous, it is faster, and the establishment does not depend on the role of individuals. The successful Korean economic model is based on an improvement-business driven to near perfection. The free trade agreements (FTAs) that Korea has engaged into with Europe and the US will help extend the success of this model in the near future; however, the FTAs also pose a direct threat to a Korean pharmaceutical industry reliant on high-priced generics for the local market. In a free market, Korean pharmaceutical will only survive if they can learn to innovate. In a broader picture, the proximity to both China and Japan as two major regional competitors further enhances the drive of Korea to lead in the innovation game. However, innovation is an especially challenging proposition for the Korean pharmaceutical sector.

The concepts of innovation and improvement are nowhere closer juxtaposed than in the healthcare field. Promising to become a future worldwide growth engine, billions of dollars have been invested into life science research in order to extricate health care innovation; however, it has been a resounding failure that has forced the global pharmaceutical companies to their knees. If the pharmaceutical industry has not completely failed, it may be because improvement has kept the businesses afloat. Like with crises in other industries, the implicit need for change and improvement can be a period of great opportunity, in particular for newcomers like Korea. However, can Korea with a relatively young research scene and a generic pharmaceutical industry, surprise the rest of the world and reinvent drug development? Of all countries, can a Confucian Korea teach the world how to accomplish healthcare innovation? The answer is yes. Despite the obvious arguments to the contrary, Korea has many unique characteristics that include dynamism, excellent education, and resilience. Above all, Korea is acutely aware of its strength and weaknesses. Subsequently, not shying away from risk, Korea embarked on a cultural experiment, inviting a French research institution to accelerate the path to innovation in life sciences. This article describes the effort and draws a preliminary conclusion on the feasibility of this approach. It describes how an entirely novel technological approach to drug discovery has been developed, and it highlights how this could only have been done in Korea. However, it also describes how cultural aspects pose obstacles to innovation in Korea.

2. CONTEXT

2.1. Innovation crisis in the pharmaceutical industry

Korea has entered the fray of biotechnology and healthcare research during a time of great transition. The pharmaceutical industry is now experiencing its biggest crisis due to its inability to innovate at a sufficient rate. The industry has survived through small improvements where existing drugs are incrementally modified to yield marginal benefits for patients. This category of 'best-in-class' new-molecular-entities (NMEs) drugs is based on identical Mechanisms of Action (MoA) and disease targets, and often employs similar chemical structures. They are modified sufficiently to gain patentable material, elicit the minimal necessary benefit for patients, and meet FDA requirements. Innovative 'first-in-class' NMEs drugs are based on new targets that represent fundamentally new MoAs with striking improvements for patients.

The risks associated with generating first-in-class drugs are higher than those encountered during best–in-class drug development. To start with, innovative drugs are based on expensive and laborious basic research. Secondly, new targets may promise significant treatment advantages; however, they often harbor hidden risks. In this context, two recent policy directions of the FDA have exacerbated the dilemma for the pharmaceutical industry. First, clinical results must demonstrate significant improvements in care that make it difficult to receive FDA approval for many of the best-in-class candidates. Second, there is increased emphasis on long-term studies even after completion of clinical Phase III trials that enhance potential liabilities for novel targets. Accordingly, pharmaceutical industry has shouldered a dual burden in its first-in-class ambitions, i.e., cover the cost for low productivity early research and assume the late stage side effect risk.

The learning curve for the pharmaceutical industry has been steep, and the increasing number of program failures has driven development costs for NMEs to the highest rate ever, with a 10 fold increase since 1975 (Datamonitor 2010). The pharmaceutical industry has reacted in a 'stepwise' development. A major strategy correction has been to disengage from early research and rely on biotech companies to bridge the innovation gap from early research to proof-of concept (POC). This has worked remarkably well for a significant period in certain markets such as the US (and to a lesser degree the UK). There, biotech companies have been able to take new ideas from academia and to translate them into innovation. About 61% of the first-in-class NMEs in the US have progressed from academia, through biotech companies to pharmaceutical companies and the patient (Kneller, 2010). With the risks of early research leveraged, the pharmaceutical industry has stoked this academia/biotech innovation engine through generous in-licensing and lucrative M&As. However, this trend has significantly slowed with the financial crisis having hit VC-based biotech start-up funding hard (Misra 2010). The woes of the pharmaceutical industry have also contributed to the decline of the biotech model. With pharmaceutical companies having less money, opportunities for lucrative mergers, or IPOs are becoming rare as VCs exit. The result is a serious innovation backlog in pharmaceutical pipelines, endangering their long-term survival

An important question is how did the pharmaceutical industry get into this predicament? It is too easy to suggest that the pharmaceutical industry has not been able to interface with academia or incorporate new trends, technologies, and insights. On the contrary, pharmaceutical research has been actively trying to make use of the human genome-sequencing project, to proteomic work, systematic gene knockout experiments in mice to genome-wide RNA arrays, and most recently RNAi. The pharmaceutical industry has also actively recruited successful academic researchers. The overall academic commitment of the pharmaceutical industry may even suggest that there has been a positivistic over-reliance on academic concepts and trends.

What has not worked is the academic paradigm that reductionist approaches can be predictive. With the completion of the human genome-sequencing project, this academic paradigm had been elevated to an industrial scale through Omics approaches. The pharmaceutical industry was captivated by the idea that the function of genes and proteins can be cornered by large-scale approaches into becoming productive drug targets. This simple reverse reductionism reflected established thinking at the time. The oversimplification was convenient for the key stakeholders in basic and applied research because it offered a convincing and straightforward rationale for researchers to secure large funding increases from policy makers. It was also welcomed by the pharmaceutical industry as it plausibly suggested a way to leverage large cash reserves into securing long-term productivity. On a more mundane level, large-scale target-based approaches were popular with a very powerful group within pharmaceuticals, namely the chemists who knew that target-structure driven drug discovery would put their expertise at the very core of the industry. Subsequently, it has taken two decades to make it clear that the tangible outcome of the human genome-sequencing project has remained negligible. It has wreaked havoc on pharmaceutical based early research. However, what the human genome-sequencing project has accomplished is the emergence of a torrent of diagnostic tools, teaching us that disease classes are not comprised of the previously suspected big coherent groups. With the help of these new diagnostic tools, the industry has been able to show significant improvements in drugs for defined disease subclasses to earn FDA approval for NMEs that might otherwise have failed. This however has been at the expense of market size that has fragmented along with disease subclasses and further deepened industry woes.

2.2. Unusable excellence of Basic Research in Life Sciences

Academia shares a similar perspective to the current crisis. Earlier academic forays into the application of life sciences have helped generate policy maker and investor expectations; however, the success stories have been simpler recombinant protein projects based on ‘low-hanging fruits’. Beyond that, academia has managed to use antiviral drug development as a translational outlet as it navigates biological space at the simplest level. Drug development on the integrated level of bacteria already pushes the predictability of biological systems beyond what is currently feasible. Tackling complex problems like cancer or even neurodegenerative diseases is beyond the reach of systematic, step-wise, and engineered therapy solutions. An exception appears to be signal transduction kinases associated with genetic predispositions towards cancer where drugs have been reported to work in a patient specific manner for a limited period before resistance sets in.

There are multiple factors that impair a direct correlation between knowledge generation and innovation. Biological systems are so complex that we can reconstruct many rules and principles; however, we cannot yet use them to predict what will happen in a complex life system. With respect to applicability, this is a principle difference to other science disciplines, where rules can be applied to predictive ends and allow the development of new materials, semi-conductors, bridges, and planes; however, it is increasingly evident in biology that we still do not understand the basic underlying rules. Gene regulation, or the study of how genetic information is regulated and used should be at the very core of rendering biology a predictive engineering discipline. However, complex, system-wide gene regulation has remained an enigma; so much so that we are still in the process of discovering new integrated layers of gene regulation even now. To mention but a few, the role of small micro-RNAs was unknown until about 8 years ago, the impact of epigenetics is barely understood today and the functional contribution of "junk DNA" was first published only two months ago. Each single one of these discoveries has chipped away at the simple and linear biological paradigm that underlies the attractiveness of the human genome sequencing project: One gene coding for one protein, which is responsible for a defined function in a live organism, a concept so simple that the identification of all genetic building stones would allow to fully reconstruct life. This form of genetic determinism is simply wrong. Life sciences are becoming ever better and clearer, but increasingly "unpredictive" in an engineering sense. At a point, however, where we face a disconnect between the quality of science and our ability to use it, the innovation engine is broken.

In this context, the expectation of universities to simultaneously produce knowledge and innovation in form of publications, patents, and revenue is unrealistic. The type of knowledge generated in contemporary academia and basic research is too simplistic to satisfy the requirements of innovation based commercial entities. In classical resource terms, this would amount to an abundance of raw oil in the face of fuel-starved industries, with no refineries in sight. Subsequently, there is a huge backlog of knowledge with an untapped pool of excellence in science. This phenomenon is currently the most striking in Europe. Continental Europe with Germany and France are second only to the US in terms of publication numbers and the science citation index. Both countries feature world leading pharmaceutical players; however, it is not possible to connect research excellence with the obvious exit in the industrial sector. The venture market still lacks liquidity after the 2008 financial crisis, biotech financing has become problematic and often leaves biotech start-ups stranded after the 1st round of financing. For several years, follow-up funding for biotech start-ups has been hard to come by and has a failure rate of 78% (Burrill & Company LLC, 2011). In an underfunded market, the biotech model becomes anti-innovative, as it under utilizes the best of research from academia. These problems have become systemic and extend further downstream as reflected by the absence of Biotech related Initial Public Offerings (I.P.O.s) in the U.S. and Europe since 2008 (Misra 2010). The productivity of the pharmaceutical market was analyzed in a regional context in a study recently published article in Nature. Strikingly, Germany does not seem to have produced more than one first-in-class NME in the last 10 years (Kneller, 2010) and implies that almost none of its basic research excellence has arrived at the application side. There are important messages to be learned from the situation. The lack of innovation is entirely disconnected from the actual quality of science; reciprocally, the improvement of the quality of science will have no im-

pact on its application.

The time has come to develop new approaches to mobilize the huge academic knowledge backlog for pharmaceutical innovation.

2.3. Korea's R&D Scene: Outstanding but fragmented

Korea is new to the scene where novel knowledge-to-innovation concepts may have the highest chance of success.

Korea provides academic research with significant funding with about a 5% a year increase (National Science& Technology Commission, 2012). Its scientists draw some of the highest salaries (relative to other OECD countries) in terms of purchasing power parity; subsequently, government and society expect an adequate return on investment. Korea has seen dramatic improvements in the level of basic research, and the output quality is on a par with Japan in several areas (Kim and Oh, 2011). Korea has high hopes for biotechnology as a future growth engine; however, Korean scientists will not be able to cover the entire distance to innovation independently. The basic biotech/pharmaceutical situation in Korea suffer from systemic problems that affect the international arena and the translation of basic research in Korea into results does not exist. The pressure on Korean academia to publish, patent, and generate revenue is relentless to the point where it may compromise the recent dramatic gains in research quality.

Another obstacle to progress in Korea is the frayed research landscape. There is no overarching operational strategy to provide traction in Korean R&D life sciences, except for the organization into individual laboratories. Independently of whether laboratories are in universities or national research institutes, the system has not permitted specialization to emerge. The Korean R&D landscape is unfortunately being leveled by a standardized evaluation system. It forces all recipients of government funds to perform according to identical standards that rank the performance of all Korean scientists in absolute terms. The impact on the research arena is far-reaching because it prevents the type of systemic asymmetry that creates synergies. Currently, service laboratories have to publish and basic research laboratories have to patent and generate revenue. Chemical institutes have to start independent biology research and biology institutes need to develop domestic medicinal chemistry. Even within institutions, laboratories have to compete with their dedicated service units (e.g. screening facilities) for the same funds. In the end, scientific units work in isolation. Despite the excellence of these individual units, larger collaborative networks like the 21st Century Frontier Program exist, but they are mostly nominal.

The operational shortcomings of Korean R&D have their roots in the brief, vigorous history of the local research culture. The standardized evaluation system may have been very useful for the initial establishment of life science R&D; however, the current level of sophistication is no longer served by this standardized system. The idea of pushing basic research towards direct applicability through an academic patent policy is short sighted and counterproductive. Korean science man-

agement has understood these shortcomings; subsequently, the Institute of Basic Science (IBS) is now being implemented. Korean academia has succeeded in convincing policy makers that pure basic research without the myopic focus on applicability is in the national long-term interest. Plans are being formalized with policies and significant funds to build a strong, independent research organization molded after the Max-Planck Institutions (MPI) in Germany and Riken in Japan. With the currently fragmented Korean R&D reality, the challenge for IBS will be to succeed in the construction of an internally coherent management and operation system to prevent the funds from being funneled back into the currently fragmented research structures. In addition to the principal problems on the predictability of life science research, Korean innovation is hampered by fragmentation, counterproductive internal competition, and the lack of an overarching vision building on the recent successes. Fragmentation and exaggerated competition prevent trust-building cohesion within the scientific community, between the scientific community, and the potential development of industry partners. The Korean pharmaceutical industry has remained an entity largely disconnected from Korean life science research. Instead, the industry has focused on generic drugs, which in the protected Korean market, has allowed the smaller to mid-sized companies to generate sizable revenues without having to innovate.

There are also striking advantages of the Korean situation compared to other key international players. Korea has funds, Korea is investing ever-increasing amounts of money into basic research, and Korea still has an existing VC scene. VC is further strength by relaxed I.P.O requirements for biotech companies on the Korean Securities Dealers Automated Quotations (KOSDAQ) that creates a viable and lucrative exit to attract foreign investment capital. The ratification of free trade agreements with the U.S. and the E.U. has created a strong willingness by Korean pharmaceuticals to open up and to work with academia to produce innovation ; however, most important is the emergence of Korean Life Science R&D. Aside from the money and research excellence, Koreans are extremely reactive, hard-working, committed, flexible, and do not shy away from risk. In building a novel Knowledge-to-Innovation concept, all these characteristics far outweigh the liabilities of a still fragmented R&D landscape. The success of such a new translational model could become the cohesive glue that pulls the fragmented landscape together.

2.4. Need for a New Innovation Engine in Life Sciences

The analysis of life science R&D and its systemic problems create a bleak reality underlining the need for of a new model for the application of basic research.

Similar to other industries, the long and complex process between academic knowledge generation and innovation has to be ring-fenced into distinct working steps, performed by dedicated specialists. With the biotech model having largely dropped out of the virtual pipeline, there is a clear and present need for a new type of institution that processes academic findings into the type of product desired by the pharmaceutical industry. Think of this new type of institution as a refinery for Korean knowledge. Only a few can cater to a large number of academic laboratories. That guarantees innovation as well as unhindered basic research. These institutions have to be publically

funded and be able to professionally master the drug discovery process with deliverables that are usable and wanted by Korean and international pharmaceutical companies to produce first-in-class NMEs.

To be able to thrive, such institutes would have to be independent of the academic evaluation systems, as the classical publication and patenting matrix would not apply. Rather, success would need to be measured by how many successful drug candidates have been transferred to the pharmaceutical industry; in addition, the task set of such institutes should be to translate the hardest and most risky part of the drug discovery pathway up to the Pre-clinical candidate (PCC), leaving the later stages (with the actual value inflection points) for pharmaceutical companies to realize revenues. Profitability, should not be a key goal. Translational institutes would leave space for a more sustained biotech model that pushes biotech companies further down the pipeline to the development stages where success becomes more predictable. Initially publicly funded, the translational institutes would later constitute platforms for public /private partnerships that attract earlier stage pharmaceutical funding as the track record of translation starts to build. Translational institutes would remain costly; however, it would be a very effective investment to finally generate returns proportional to the massive basic research investment of funds.

A new translational entity would have to be able to address the largest systematic liability of current drug discovery and would have to develop technologies that would render progress independent from the failure of large-scale, target-based drug discovery. It should be possible to use basic research without having to rely on simplified predictive models.

These operational characteristics and hallmarks were at the core of the design of IP-K as a new model institute for 21st century translational research needs.

3. BUILDING A NOVEL TRANSLATIONAL MODEL IN KOREA

3.1. Conceptualizing an Institut Pasteur in Korea

IP-K, as a new pristine institute, offers a unique opportunity to adapt the position of an institute to the changed long-term outlook that can simultaneously address the principal needs of stakeholders. The IP-K outline is:

We planed an institute that carries the mission of Louis Pasteur into the 21st century:

- IP-K had to be able to use fundamental research in order to drive application oriented programs; subsequently, new translational technologies and approaches had to be developed. IP-K's research outcomes had to impact patients.
- IP-K had to play a new role as a translational vehicle between academic research and pharmaceutical companies. It is to supplant the previous Biotech model and create value from pure basic research.

IP-K was designed to address the key expectations of stakeholders:

- For Institut Pasteur it constitutes a unique chance to outsource the establishment of an application driven institute with a focus on tangible therapies. Addressing patient needs helps IP to readjust its long-term mission closer to the original roots

- For the Korean government and Korean science management, it creates a new model to generate basic research value. It takes the pressure from academia to combine basic research and desired application, leaving the latter part to a specialized partner, IP-K. This is timely and compatible with the establishment of IBS.

- For pharmaceutical companies it constitutes a unique chance to gain access to academic research in a useable form. The publically funded translational research model would help offset the diminished Biotech role and simultaneously alleviate the costly reliance on internal basic research

These three aspects address the changed outlook in the healthcare arena, promise a sustainable long-term model for academia and pharmaceuticals, and generate revenues from the investment of public funds. Beyond these major criteria there are other benefits to be reaped from a successful IP-K model. It constitutes a unique experiment, where the Korean government hosts an international collaboration to produce research innovation. This allows the learning of an important lesson in the management of international projects and in studying the anatomy of innovation oriented science management.

3.2. Inventing Technology to Innovate Drug Development

The IP-K model has profited from a radical break of context from other global research institutes. This offered the chance to build an institute at the fault line between innovative research and therapy-based applications. All aspects, from R&D planning to operation and management, are new and distinct from traditional academia or Biotech set-ups. The result is an IP-K that effectively transports the Pasteurian concept of 'translational' research and development. IP-K creates synergies between the opposing objectives of basic science and application; IP-K's organization and operational layout have created a new environment in which application drives basic science.

The key distinction of the IP-KsK approach has been to move away from predictive paradigms. Instead, of predicting the role of genes and proteins in complex systems, IP-K has turned the process upside down. IP-K scientists observe which drugs work in a complex live system, and then reconstruct, which gene or protein has been targeted by the effective drug in a second step. The approach is built on recent advances in live imaging. These allow visualizing that allows the visualization of the effect of chemical compounds in live cells. Such live models can be very close to actual disease such as infectious mycobacteria that invade and replicate in live human immune cells (in this case macrophages). In this specific example, visual screening allows the identification of chemicals that stop or kill mycobacteria in human macrophages, without being toxic to human cells.

IP-K had to pioneer many novel and challenging steps in order to perform drug screenings with actual live disease models. First of all there was the overriding issue of safety because infecting live cells with infectious TB strains had never been done before. IP-K had anticipated this challenge by placing the screening equipment into a high security Biosafety Level 3 laboratory[2], the first of its kind. The original containment lab was constructed around screening robotics boxed up in the center of the construction side. The next challenge was to mold the screening steps into a coherent process that combines three independent modules: 1) Visualization of disease steps, 2) Live imaging and 3) Ultra-high-content/high-throughput screening. The problem was the magnitude of data that had to be managed in a centralized and effective fashion; subsequently, IP-K established a dedicated imaging group. This group engineered an integrated and effective dataflow. Individual disease models are intrinsically different from each other and the imaging specialists had to develop dedicated algorithms for each program to extract, assess, and quantitate all visual effects that thousands of chemical compounds would impose on a live disease model. Integrating these three elements into a coherent workflow, IP-K became the first entity world-wide to run imaging based high content screens as the primary approach. IP-K has rendered drug screens 'target-free' in a complete reversal of conventional thinking through the combination of IT with BT. The visual, target free approach is called PhenomicScreen™.

The ensuing challenges hit IP-K successively, as its drug discovery programs started to advance along the drug discovery pipeline. Some of these challenges were deeply implied in science culture. For example, IP-K medicinal chemists had to start optimizing the structure activity relationship (SAR) of a drug candidate without target knowledge and deviated from established wisdom in target-based drug discovery. However, the long-term success of PhenomicScreen™ with increased efficiency critically depended on the ability to perform SAR without target knowledge. From 2006 onwards, IP-K began building its internal medicinal chemistry capacity in collaboration with the visual screening and IT groups. Together, they successfully pioneered target-free SAR through iterative optimization cycles and visual screening groups. The IP-K approach was shown to be superior to traditional target-based approaches. Also, drug candidates from live cell primary screens can have superior druggability and better pharmacokinetic values. Further, aspects such as permeability and affinity are automatically included in cell-based SAR. These combined competitive advantages offset the IP-K drug discovery approach and signify a lead over the competition in Biotech and pharmaceutical companies.

Another innovation push arising from PhenomicScreen™ was in the area of target identification (ID). Although target-free drug discovery is feasible, effective, and very fast, the knowledge of targets is eventually beneficial for drug development and the understanding of underlying disease mechanisms. In 2007 and 2008, IP-K engaged in the development of an entirely innovative

[2] A Biosafety Level 3 Laboratory (called Containment Level 3) is designed for work with risk Group 3 microorganisms and with large volumes or high concentrations of Risk Group 2 microorganisms that pose an increased likelihood of aerosol spread. A Biosafety Level 3 Laboratory requires the strengthening of the operational and safety programmers over and above those for basic laboratories.- WHO 2004 Laboratory biosafety manual

target ID approach, using a drug candidate to directly zoom in on a target. The approach involved a combination of hardware development in the form of printed glass wafers, reading equipment, and innovation in automated visual annotation programs. The combined efforts of the two teams finally had a performance breakthrough in early 2008 with high resolution, visual imaging screens on live cells that took only 8hours, on a genome-wide scale. IP-K, now performs target ID work faster and more accurately than any other entity in the world. The successful development of this approach, named PhenomicTD™, ideally complements PhenomicScreen™ and target-free SAR. IP-K is now a world-wide drug discovery leader.

IP-K manages a new paradigm in drug discovery that is faster and more effective than any other available approach. The new paradigm links to an earlier period when Drug discovery was mostly based on empirical observation in the first half of the 20th century. Phenomic technology enables IP-K to observe empirical evidence. In the meantime, visual screens have become a routine operation elsewhere in Biotech, pharmaceuticals, and academia; however, in contrast to IP-K, other entities cannot use visual approaches in their primary screens and lack target identification technology as well as capacity.

3.3. Creating a novel translational context in Korean R&D

IP-K opened the possibility of mobilizing large areas of basic research for application through the use of technology that can engage in target-free basic research. To live up to this potential, IP-K started to streamline its internal operations by hiring key personnel from the pharmaceutical industry, by introducing a matrix based management system, and milestone driven programs. The funding emphasis shifted from research and method development to discovery capacity with an increase in the medicinal chemistry group as well as the establishment of drug metabolism and pharmacokinetics (DMPK). The result is a research institution that resembles a biotech in structure and goal setting.

- With the capacity to translate up to 8 new projects per year, IP-K began close discussions with the Korean government around a novel system to draft academic research into the translational engine of Translational Project funding. Funds are made available to translational institutes to invite promising academic projects to join a collaborative discovery program over a limited period of time.

- Simultaneously, IP-K began working with the pharmaceutical industry on a fee for service basis in order to establish phenomic technology. After 3 years, several major pharmaceutical companies had direct (or indirect) collaborations around the IP-K technology platform. These have extended into extended scientific discovery collaborations.

- IP-K began to establish its own Biotech entity and create its own context that allows for the further development of projects. Qurient Therapeutics[3] can move projects into Phase IIA. It has successfully secured funding through Korean and international VC firms and is

currently finishing Round B of financing.

IP-K has leveraged its unique phenomic technology to create a coherent collaborative context, and position itself in between Korean academia and the Korean pharmaceutical industry. In a first successful case study IP-K managed to bridge an infectious disease model from Yonsei University and an international pharmaceutical company represented in Korea. IP-K has fulfilled the key expectations that the situation commanded:

- The development of dedicated phenomic technology has enabled IP-K to use fundamental research to drive application-oriented programs.
- IP-K has been able to play a new role as a translational vehicle between academic research and pharmaceutical companies.

Together this creates a potential continuum in the flow from basic research knowledge providers to innovation users on the other side of the innovation gap. It brings the promise of cohesion and productivity to the fragmented Korean R&D landscape. IP-K has succeeded in developing a feasible new knowledge-to-innovation model.

3.4. Benchmarking IP-K against the leading international translational institutes

The concept of translational drug discovery has increasingly moved into the forefront of science policy. In general it shares definition of IP-K to translate basic medical science and research into drug or therapy candidates with clear clinical benefits for patients. It clearly differs from the clinical translation concept and represents a quintessential goal of basic research investment by society. This type of translation has become a global reality. In Germany, the Lead Discovery Center (LDC) in Dortmund opened its doors in 2008 and now does translating research for the roughly 50 Max-Planck Institutes active in the life science area. The Center for Drug Research and Development (CDRC) in Vancouver has been translating for the University of British Columbia since 2006, and the Center for Translation at Scripps Florida has been in operation since 2005. The Institut Pasteur Korea (an entirely Korean institution) is not only one of the first to actually have realized the translational concept in 2004, it is one of the only entities that have developed a technology to purpose and allows the possibility to engage academic projects in the translation process at an earlier time point. This represents a new model and a new technology – Innovation made in Korea. Korea spearheads a novel concept that carves a more effective flow from knowledge to innovation and constitutes a competitive advantage in harnessing life sciences as a growth engine. To underline the achievement of Korea in this arena we have benchmarked IP-K vis-à-vis other leading international translational entities:

[3] Qurient is a spin-off biotechnology company from Institut Pasteur Korea dedicated to develop novel therapeutics

U.K. 2002, Cancer Research Technology (CRT): UK-based CRT is a fully integrated drug discovery outfit for early-stage cancer projects. Backed by a foundation, CRT can incubate basic research projects all the way to preclinical development. CRT is a success story, with several industry licensed projects that entertain large-scale industry collaborations with pharmaceutical companies like AstraZeneca.

Belgium 2006, Center for Drug Design and Discovery (CD3): Leuven-based CD3 is an initiative of the technology transfer unit of the University of Leuven, Belgium. It still is a department of the tech transfer office. It has industry-standard medicinal chemistry capabilities and is considered a validated translational institute since it managed to incubate and license projects of academic origin.

Canada 2007, Center for Drug Research and Development (CDRD): The CDRD is a highly successful platform that performs translational work for academic institutions in British Columbia and beyond. Funded in the range of 60Mio US from private public partnerships, the CDRD has engaged in a close collaboration with Pfizer as a major exit strategy provider for successful projects.

Germany 2008, Lead Discovery Center (LDC): Max Planck and Max-Planck Innovation GmbH have entered the fray with the Dortmund-based Lead Discovery Center GmbH (LDC). Its pharmaceutical trained staff is successfully distilling Max Planck's basic research excellence into small molecule drug precursors. The LDC goal is to convert basic research findings in close collaboration with the academic project owner (principal investigator) into leads with POC in animals. Only 3 years in place, they have successfully produced three such leads on different molecular targets. One of the leads was subsequently licensed to Bayer Schering.

UK 2009, Medical Research Council Technology (MRC-T): UK-based MRC-T is a small molecule drug discovery organization and backed by national funds. MRC-T entertains industry collaborations and produces leads, based on basic research results. As for the other centers, leads are available for licensing to pharmaceuticals and Biotech. MRC-T has to be considered validated, since they have licensed out several of their products.

US 2011, National Center for Advancing Translational Science (NCATS): Following a previous engagement in the area of Therapeutics for Rare and Neglected diseases (TRND) the NIH expanded its investment into translational work through the establishment of the National Center for Advancing Translational Sciences. This engagement of the NIH stresses the strategic need for application oriented research models beyond Biotech. It is an extension of the NIH roadmap that has outlined the principles of translational activities within the confines of the NIH in 2006. Academic drug discovery has spread to over 56 different universities that have small to significant drug discovery capabilities (Frye et al. (2011)). Among the prominent and fully integrated players in (early) drug discovery are Scripps Florida, Sloan Kettering, and Dana Farber.

The planning and positioning of IP-K as a translational institute has been visionary, with

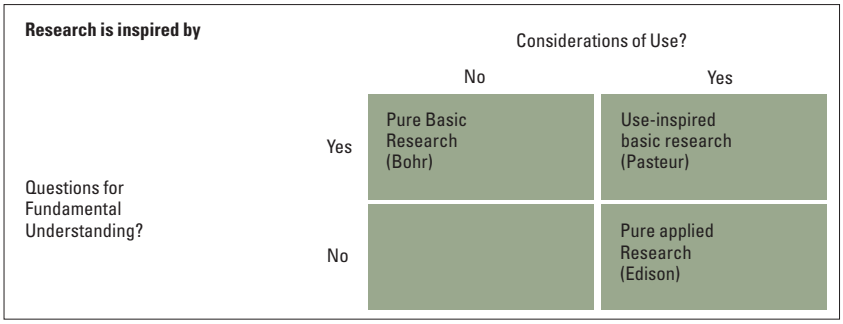
only the CR-T having started earlier. The strategic choice by the IP-K has been vindicated by the emergence of key global institutes, the latest being the NCATS by the NIH. The decision of the IP-K of to approach translation with high content visual screening has been forward-looking and is now vindicated by developments in Biotech and the pharmaceutical industry. There are other key advantages of IP-K. In contrast to all of the other translational outfits, IP-K is not an appendix to a larger basic research organization. It performs translation in its own right. This is a striking difference because IP-K has to compete for knowledge providers. It is the only institute that has developed custom made technology for translation. It helps IP-K attract knowledge providers beyond its own backyard. This constitutes an advantage for Korea in the ability to import and commercialize basic research developed and financed by outside countries. IP-K technology offers three key advantages over other institutes:

1. Research can be taken from the bench before the identification of targets. The consequences are far reaching. The IP-K translation engine can engage academia earlier and address a broader academic basis. Following the 'Quadrant Model' (see below), IP-K can tap into the 'Bohr Quadrant'; however, all other entities have to start from the 'Pasteur Quadrant' as knowledge providers. The latter allows for a faster start; however, IP-K's investment in technology development provides more depth, is more compatible with fundamental research, and can eventually generate more value.

2. The phenomic approach of IP-K drives the drug discovery process from effective compounds as starting points. It identifies targets as a secondary step. This predestines phenomic discovery for new targets and first-in-class compounds, this is where the pharmaceutical industry has the biggest demand. The implicit novel MOAs constitute excellent starting points for innovative basic research.

3. The unexpected Phenomic lead optimization as implemented in IP-K has many advantages and allows a fast lead discovery. Cell-based lead optimization automatically factors in several of the lead optimization steps.

FIGURE 1. Quadrant model of scientific research



*IP-K is currently the only translational institute that can effectively tap into the Bohr Quadrant as a knowledge provider. This is based on its unique phenomic technology. The Bohr Quadrant is and area of research to be significantly strengthened in Korea though the establishment of the Institute of Basic Science. * Note: Stokes (1997), Pasteur's Quadrant, p. 73.*

3.5. IP-K: A new, leading model for Life Science Innovation made in Korea

With IP-K, Korea has pioneered a new model of a translational institute that is able to mobilize basic research for pharmaceutical application. Custom made technology is ideally suited for this task as it is non-predictive and target-free. This opens a wider base of basic research for translation and moves drug discovery away from the failed target based reductionist approaches.

IP-K has further established a successful new form of implanting translational institutions into the R&D landscape using dedicated funding tools. Overall, this segments the pathway from basic research to the market into ring-fenced and highly specialized working steps, liberating academia to concentrate on basic research. Simultaneously, it creates the possibility to generate value to basic research in a focused, specialized entity, value that in the case of commercialization will be shared with the early research base.

In assigning, asymmetric and dedicated tasks to different types of institutions, science management increases synergies, the overall efficiency of the R&D system, and coherence in a focused collaboration scheme. On a national level, it increases the return of investment for basic research and enables pharmaceuticals to upload first-in-class-drug candidates without the risk and cost of early research. The IP-K model addresses the key issues that underlie the current crisis in life sciences and pharmaceuticals.

The operational success of IP-K as a translational model offers unique opportunities to Korea at its very moment of development. It can help create value to the massive future investments in pure basic research in the form of IBS; however, by financing first-in-class drug discovery, it can assist the pharmaceutical industry by absorbing the double shock of free trade agreements and pricing policy through providing innovative, first-in-class drug candidates made in Korea.

4. LESSONS LEARNT FROM AN INTERCULTURAL COLLABORATION

4.1. Korea, an accommodating and effective host

The implementation of IP-K has been a truly intercultural experience. European researchers have come to build an entirely novel institute in Korea within a relatively wide framework. The project was not micro-managed from Paris, nor does Pasteur have a corporate SOP for the establishment of international institutes. Guiding principles for the set-up of the IP-K were a combination of Pasteurian core values and the very clearly defined translational mandate “From Genes to Drugs”, given by the Korean government. The detailed execution was delegated to the team in Korea as allowed for space to fit the new institution into the cultural, academic and economic context of Korea. The European management team was physically present in Korea full time, with several members having stayed more than 5 years. This last point is the most tangible difference versus other foreign institutions moving into Korea.

A close dialogue ensued in the initial period of interaction between the fledgling IP-K and the Korean authorities. There exists a very strict framework of rules and regulations around national research institutions in Korea; however, it was possible to customize solutions for IP-K whenever this was critical for the project. This then allowed the creation of a truly new and unique institute, different from Korean research institutes that are also unique by international standards. However, the uniqueness IP-K remains very Korean. As a first milestone, the dialogue with the Korean government helped form a foreigner support system that effectively caters to the needs of foreign specialists in Korea. Together with the highly competitive salaries (by OECD standards) and tax incentives from the Korean government, IPK was able attract the exact portfolio of international specialists it needed. Their expertise was complementary to the mainstream of science and technology available in Korea at the time. These new human resources were cell biologists, imaging and screening specialists, and robotics experts. Foreign experts, with an average stay of 2.5-5 years, have been in sufficient numbers and commitment to transfer their unique expertise and expertise to Korea. The close interaction with the Korean government was able to find solutions to most problems; however, one critical point that could not be changed was that the IP-K project was financed within the Korean Government 21st Century Frontier program. The funding source entailed an evaluation criteria traditionally used for Korean Government research laboratories and evaluation teams that consisted primarily of Korean academics.

The IP-K experiment has created innovation – 'Made in Korea'. The reasons for the creative productivity of the first years of the IP-K are mostly intangible. However, the framework conditions with elevated and focused funding, highly ambitious goals, and quasi-academic settings have been essential. Other factors have been equally indispensable such as the transfer of technology. The most cutting edge ideas of Institut Pasteur at the time, i.e., the visualization concept and technology were transplanted into IP-K and developed to scale. Another factor has been the 'freedom-to-operate'. The management of IP-K was left unhindered by stakeholders to implement the basic structures into place and realize the concept of phenomic translation in a single-minded manner. A more intangible criterion for success has been an atmosphere of 'splendid isolation' where IP-K scientists were bound to succeed after their arrival. There was immense pressure to get phenomic technology and new approaches to work. The pressure was compensated by appropriate funding, an exciting and innovative strategy, a sense of companionship in a competent setting, and an extremely energizing and dynamic environment. The typical layer of detractors, 'nay-sayers', and pessimists that would have accompanied a similar project in Europe simply did not exist here; instead, the atmosphere was of enthusiasm and relentless hard work by the Koreans. It was this splendid isolation that has allowed IP-K scientists to come up with several feats that were deemed impossible by pharmaceutical critics. Target-free phenomic screening had been tried before, but without success. Target-free SAR was considered impossible and unacceptable, and target deconvolution simply did not exist.

4.2. Fostering innovation: The Korean shortcomings

IP-K had to face initial cultural conflicts; however, at a superficial level. There was a tendency of

foreign researchers to underestimate the capacity of their Korean colleagues; a prejudice that was rapidly and thoroughly corrected. It was reciprocated by the Koreans who considered foreign researchers as lazy because they would not work typical Korean 14 hour workdays (unfortunately, that notion still lingers on today). Another more serious problem was asymmetry in a hierarchic distribution of IP-K, in particular in the first years when most of the leading positions were filled by foreigners. The reasons were a lack of specialists in the key areas as well as the hesitation by excellent Koreans to move to a novel institute that only offered time-limited contracts. The hierarchy issue was exacerbated by certain privileges that foreigners were granted, in particular with respect to taxation. With time the issues dissipated as the hierarchic distribution became more even and the tax privileges were largely revoked. Lastly, these issues slowly moved into the background with a shared buy-in into the goals of IP-K.

More serious cultural problems existed in the second phase of IP-K. These problems were profound and subtle at the same time, and they seriously threatened the overall project. At a point when IP-K had advanced with both its technology and translational concepts to where success seemed inter-subjective, it became clear that there was no appreciation or understanding of the abstract advantages of our strategy. There was no understanding for the conceptual upsides of our technological approach or for the non-figurative aspects of the long-term translational plan. There was even less grasp of the long-term tangible and intangible potential of phenomic translation for the Korean R&D landscape. This cognitive dissonance was almost ubiquitous on the Korean side, starting from several staffs at IP-K to outside academia or the government. With few exceptions there was no propensity on behalf of the Korean partners to extract the essence of the IP-K project.

Intriguingly (as far as IP-K staffs were concerned) this did not detract from their dedication or productivity. On an anecdotal level, it was disconcerting that (for example) after several plenary meetings with endless explanations of IP-K concepts and goals, Korean researchers kept wondering about the concepts and goals. It was not an intellectual problem in grasping these concepts, but rather that the Korean staff could not attribute a special weight or significance to them. These goals seemed abstract and irrelevant. By contrast, the Korean staff appeared more focused on tangible issues, their team vis-à-vis other teams, rank, title, and relative performance. European and Korean researchers worked together at IP-K on the same projects and programs, but were able to see different realities in them. It became tentatively clear, that for the Korean partners abstractness was not in very high regard, which is in pointed contrast to the French scientific culture.

Despite these cognitive dissonances, it seemed that there were sufficient objective facts to underwrite the success of IP-K. There was an entirely new technology that had passed proof of concept, there were new collaborative structures with academia, multiple collaborations with international pharmaceuticals, a VC funded spin-off, and a leading new TB drug in the pipeline. Most importantly, there was that huge potential of IP-K as a new translational model in the Korean R&D landscape; Hence, with, the achievements so obvious, IP-K undertook only little PR efforts to communicate the results. This was a major management mistake and it became clear when the IP-K was eventually evaluated by its peers in Korean academia. With little information on the nature and characteristics of IP-K, the evaluation was subjected to a purely numeric, standardized

performance system, and treated the IP-K as a 21st Century Frontier Program. Evaluations did not take into account that translational institutes are not intended to publish. It did not appreciate a conservative value oriented patenting strategy. It certainly did not have any categories to weigh novelty and innovation potential, two aspects that remained irrelevant throughout the procedure. As a result, the evaluation by Korean peers was catastrophic. Looking at IP-K through the lens of standard procedures, the institute looked inadequate in all categories. By contrast, evaluations by international evaluators were extremely positive. They highlighted the achievements in technology development, operational excellence, the huge potential of IP-K's strategy, and the translational approach. In 2010, the IP-K scored the second highest evaluation by NIH standards in a mixed international evaluation versus the second lowest by Korean standards. Both evaluations paradoxically represented the true value of IP-K from a Western or a Korean viewpoint. In the 2010 stage of development, IP-K simply had no visible quantifiable value to Korean reviewers. The Korean academic evaluation system is not designed to see abstract innovation because it is by definition new and cannot be benchmarked. Nascent innovation remains abstract over an extended period of time, a period through which value exists only as far as the presumed strategic future target is shared and understood; however, this does not exist in Korea. In preempting the outcome, innovation can appear on the radar of Korean evaluation only indirectly through what it produces or causes (preferably revenue) but possibly also other manifestations of success as long as they can be quantified; however, this usually does not happen until late in the innovation process. It is hard to imagine then how genuine innovation could emerge under this system.

4.3. International collaborations in Korea: The Innovation Fast-Track

If the realization of apparent cultural differences in R&D seems far-reaching, there are two points to remember. IP-K is a very unusual experiment that amplifies otherwise hidden subtle cultural differences. In particular (in the context of its preference for abstraction) France is at the very opposite range of what appears to be true for Korea and differences are then bound to develop. The other point to keep in mind is that qualities and capabilities usually come as a tradeoff; therefore, the Korean adversity to abstraction is effectively compensated through linear and goal-oriented pragmatism.

This brings us back to the beginning chapter of this article: Innovation starts as an invention, in an extended process that is adopted by markets or society. Looking at the IP-K experience, there are systemic problems in the evaluation of the potential associated with invention in Korea and fostering for market consumption. In France, by contrast, it is straight-forward for society and decision makers to realize the innovative potential of an invention; however, it is operationally and practically impossible to move an inventive program towards the market. There is an obvious cultural complementarity in this, which is at the core of the success of the IP-K project. What has been striking in the IP-K experience is that as soon as phenomic technology began to materialize, the Korean 'improvement-machine' kicked in. It was highlighted where performance needed to be improved at each stage of the evaluation. This was accompanied by sufficient funds, by extremely hard working ethics, by flexibility in the creation of a Qurient spin-off (or alternative funding programs) by suf-

ficient venture capital funding. Goals and milestones were defined to be met throughout the project with a pragmatic efficiency unimaginable in Europe. IP-K underwent constant improvements that eventually led to a level of performance it can now be proud of. The potential of IP-K was not initially understood by Korean partners; however, they nonetheless catapulted the institute down the path towards the goal line.

5. CONCLUSION

IP-K represents a Franco-Korean study case for cultural complementarity towards creating innovation. Subsequently, Korea has one of the most advanced global translational institutes, and a technological platform that (if properly positioned) can greatly move towards the ambitious goals of the bio-industry area. However, France has transferred key technologies and some of their best researchers who have learned that (when consistently improved and implemented) their abstract ideas can become a feasible reality. As a consequence, France will re-import the IP-K concept as a translational institute.

It makes sense for Korea to continue along the path of international collaboration by inviting other partners to join or by expanding IP-K as a bridge-head and nucleation site for extended international collaboration in the life sciences arena. In the meantime, to improve the innovation environment, it is crucial for the evaluation system to become nuanced and to be able to assess the strategic potential of projects. One way to get there fast is to build an infrastructure of mixed international evaluations throughout the Korean system.

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