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The strength of collaborative research for discovery in Horizon 2020

Key messages

- Research is the backbone of Europe's competitiveness and the broad spectrum of research undertaken at research universities lays the foundation for a wide variety of discoveries and innovations leading directly, circuitously, or serendipitously to economic or societal benefit and industrial exploitation. Often innovations - in the sense of the practical exploitation and application of new ideas in real life - cannot be predicted from the initial stages of fundamental research. All fields of research contribute to this process, from the arts and humanities, to the social, natural and life sciences and engineering, each making their own contributions, regularly in dynamic patterns of interaction, interdisciplinary work, and collaboration.

- This LERU Note focuses on "discovery research", which we define for the purpose of this Note as fundamental or frontier research that is directed toward greater knowledge or understanding of the fundamental aspects of phenomena and executed without foreseeing a practical end goal, without *a priori* specific applications or products in mind. This type of research, which is primarily concerned with asking essential scientific questions and with deciphering basic processes or mechanisms, has laid the foundation for technologies in the past, and will continue to be essential for innovations that Europe will need in the future even when it cannot yet envisage, let alone commission them.

- Most research is increasingly or already highly collaborative in nature. Collaborative research appears in many shapes and degrees of more or less structured formats, for example through extremely large or very small research teams, through team science, international networks, informal exchanges and more. Indeed, it is at the heart of the EC Research Commissioner Carlos Moedas' "open science, open innovation, open to the world" strategy. Collaborative research is of vital importance in discovery research, bringing together specific expertise, resources and equipment from different disciplines and various places. Its potential

benefits have long been recognised, bringing about, for example, novel approaches, higher research impact, and improved innovation through cross-fertilisation.

- Collaborative discovery research is essential for Europe to be at the forefront of innovation and to deliver economic and societal impact. At the EU level, collaborative discovery research is supported mainly via pillars II and III (Industrial Leadership and Societal Challenges, respectively) of Horizon 2020, the EU's framework programme for research and innovation. However, calls for research proposals in these programmes often stipulate *technology readiness levels* (TRLs) and funding decisions are disproportionally skewed towards projects at the higher TRLs (five and above), which compromise opportunities for the most innovative projects and can lead to risk-averse approaches to economic and societal impact. It is recognised that collaborative discovery research is possible via the Future and Emerging Technology (FET Open and FET Proactive, in particular) scheme in pillar I (Excellent Science). In fact, the oversubscription of the FET scheme illustrates the opportunities that it could bring to pillars II and III of Horizon 2020.

- A programme of collaborative discovery research is essential, within pillars II and III, for potential longer-term societal or technological relevance or impact. LERU believes the focus on TRLs within these programmes undermines a much needed, strong and continuous investment in collaborative discovery research, not only between research institutes but also between universities and industrial research development laboratories. Unintentionally it could be limiting the opportunities and potential for strengthening and widening Europe's research capabilities by failing to build bridges between research laboratories across all sectors addressing discovery research. It needs to be urgently reviewed to ensure that low-TRL collaborative discovery research in Horizon 2020 pillars II and III is not neglected and that the goals and the measures of success are not always driven by short-term returns.

- It is recognised that vital opportunities and major benefits are derived from investigator-based research in Horizon 2020 and earlier EC research framework programmes, in particular through open-ended, bottom-up mechanisms such as the European Research Council and the Marie Skłodowska Curie Actions. LERU strongly supports these, as well as the FET scheme. These schemes are vitally important for Europe to remain at the leading edge of globally competitive research and LERU does not wish to see their success jeopardised.

- In the longer term, LERU would like to see new approaches for future EC research programmes to better target collaborative discovery research, delivered through a broad range of partnerships in both the public and private sector, that do not focus purely on short-term future technological applications. In the face of global competition for research talent and resources, there are great benefits to be reaped from Europe investing in collaborative, transdisciplinary and trans-sectoral discovery research to produce scientific breakthroughs and paradigm shifts.

- In addition, it is vital that national funding agencies also acknowledge the utmost importance of distributing funding in a balanced way between fundamental and translational research, which have contributed so much to the progress of our societies in the past.

Introduction

Discoveries in all scientific disciplines are essential for societal and industrial development; often the societal impact that eventually results is not well defined from the onset. History indeed has shown that breakthrough discoveries build on the unexpected, a phenomenon named *serendipity*. But also research that addresses important scientific questions can ultimately lead to transforming discoveries far beyond applications perceived at the time. Well-known examples from the natural sciences include the discovery of electricity, the voltaic pile, transistors, the structure of DNA, antibiotics, magnetic resonance imaging, lasers, giant magneto resistance, light emitting diodes, etc. At the time of discovery, their broad usage was not yet (fully) anticipated. For many of these inventions decades of meticulous targeted research have passed between the lab discovery and economic benefit or industrial exploitation (LERU, 2011a, 2011b; KVA, 2012).

While it is crucial to exploit research to directly solve short-term societal and commercial questions, it is also of utmost importance that a significant share of research funding is allocated to frontier research across all disciplines that is not primarily aimed at specific short-term commercial or societal benefits. The balanced co-existence of discovery and enabling research with pre- and post-competitive applied research has served as a springboard for a multitude of transformative innovations in the past and will continue to do so in the future in all areas of science. To illustrate this by some well-known examples, the scientific history of magnetic resonance imaging, the mobile phone, scanning probe microscopes, and monoclonal antibodies is briefly described in the appendix. Similar examples are readily available across all disciplines of natural sciences, but likewise in engineering sciences, biomedical sciences, social sciences, and the humanities.

Discoveries may be the result of a process where essential purely scientific questions are tackled by multi-disciplinary frontier research, often relying on collaborative efforts. Some of these discoveries may turn out to be stepping stones toward innovations leading to industrial applications or societal impact bringing societal and economic benefits. Obviously, in reality the process of valorising research is not always linear. Also, quite a lot of research does set out with specific application goals in mind. One also needs to acknowledge that not all basic research will end up being 'useful' or applied later on. In his recent report to the UK Government (BIS, 2015), Nobel Laureate Professor Sir Paul Nurse remarked that "discovery, translational and applied research should not be thought of as completely distinct. The boundaries between them can be blurred, with discoveries being made during applied research and applications emerging during discovery research. Nor is it correct to view it as an unidirectional process, moving from discovery through to application – knowledge transfer occurs in all directions. What is important, is that all three modes must be pursued if a national research endeavour is to be effective in bringing about social and commercial benefits." This obviously is also the case for research efforts at a European scale.

The most important European funding scheme for research and innovation is Horizon 2020 (H2020), which consists of three pillars: I) *Excellent Science*, II) *Industrial Leadership* and III) *Societal Challenges.* With both the European Research Council (ERC) and the Marie Skłodowska Curie Actions (MSCA) in

pillar I, there is a clear place for investigator-driven frontier research in H2020. These schemes aim at funding excellent *individual* researchers and their teams. LERU has been a staunch supporter of the ERC approach and wants it to remain a vital and strong part of the EU research programmes. Another valuable funding opportunity in H2020 is the Future and Emerging Technologies (FET) scheme and especially the FET Open instrument, which deals with disruptive technological research where applications are already anticipated or known. While highly solicited, FET success rates are extremely low (in the few percent range).

The two other pillars of H2020, Industrial Leadership (IL) and Societal Challenges (SC), fund research projects on predefined, broad themes including ICT, Health, Climate and Energy. Industrial Leadership supports innovative small- and medium-sized enterprises in speeding up the development of technologies that are already close to the market. The Societal Challenges pillar, on the other hand, is aimed at the development of new solutions for specific challenges confronting Europe, such as ageing, transport and food production.

As Professor Sir Paul Nurse recently observed: "The most effective research systems at producing knowledge for the public good are characterised by freedom of action and movement: they need to be permeable and fluid, allowing the ready transfer of ideas, skills and people in all directions between the different sectors, research disciplines, and various parts of the research endeavour" (BIS, 2015). This multidirectional approach, however, is not fully realised by the current H2020 funding schemes.

The strength of collaborative research for discovery

Nowadays, frontier research is often, albeit not necessarily, collaborative in nature, manifesting itself in a variety of more or less structured formats. Collaborations between researchers and research groups across borders have become more important than ever, due to the increasing complexity of scientific and societal questions. Multifaceted questions need multifaceted approaches, sometimes coming from one scientific discipline but often transcending the boundaries between disciplines. All parties involved in collaborative research bring their specific expertise and strengths into the project, producing a cross-fertilisation that results in answers and solutions that could not easily have been generated by a single research group alone. Research may be performed in well-connected teams, but also seemingly isolated scientists and groups profit from global progress that is made in (sub) disciplines and which is readily available through open access scientific literature. As such, collaborative research fits well within the European Commission's current research strategy, which is to chart a new path for "open science, open innovation, open to the world", according to Research Commissioner Carlos Moedas[1].

Collaborative research often exploits infrastructures, particularly in the natural sciences. The Large Hadron Collider and CERN, based in Geneva, are prime examples of very large collaborations that have led to Nobel prize winning discoveries. Increasingly, collaborative data infrastructures are set up, not only in the natural sciences but also in the humanities, social sciences and life sciences.

The role of research teams across nations and disciplines is starting to be better understood and recognised. For instance, the UK Academy of Medical Sciences has set up a "Team Science" project "seeking to understand the current incentives and disincentives for individual researchers participating in 'team science', and how to improve

1 http://europa.eu/rapid/press-release_SPEECH-15-5243_en.htm

reward and recognition for their contributions"[2]. It lists well-recognised benefits of team science, such as achieving higher research impact, better correspondence to global challenges, clinical trials or translational work, improved innovation through cross-fertilisation, and improved development of new methodologies. Benefits to the researchers involved include: involvement in more novel research and more impactful research, acquisition of new skills, improved opportunities for networking, and greater sharing of risk.

Clearly, there are important benefits to collaborative research. The collaborative approach has long proven its value in pre- and post-competitive applied research and has become invaluable in discovery and enabling research as well. The ERC Synergy Grants under FP7 are an example of the recognition of this approach by the European Commission. Collaborative research is a cornerstone of the Industrial Leadership and Societal Challenges pillars in H2020, whose purpose is to generate many of the answers that tomorrow's society needs and many of the insights that tomorrow's technologies will build on. It should be recognised that collaborative discovery research has a lot to contribute to both the IL and SC pillars.

The current limitation to discovery research imposed by TRLs

Unfortunately, funding opportunities for *collaborative discovery* research are at risk, increasingly squeezed out because of policy makers' and funders' current focus on fast innovation and economic and societal impact. The EC's H2020 research programme is no exception to this. In its current implementation scheme, the funding of collaborative discovery research within the priorities laid out in the H2020 work programmes is seriously hampered by the *technology readiness levels* (TRLs) that are specified in the calls for proposals[3]. TRLs indicate the desired level of technological maturity of a proposal, ranging from TRL 1 (basic principles observed) to TRL 9 (actual system proven in operational environment), and where anything below TRL 4 is technology that has not been validated yet, as shown in Table 1. The focus of this Note is precisely on the lack of opportunities for collaborative research in H2020 at the lowest TRLs.

- TRL 1 – basic principles observed
- TRL 2 – technology concept formulated
- TRL 3 – experimental proof of concept
- TRL 4 – technology validated in lab
- TRL 5 – technology validated in relevant environment (industrially relevant environment in the case of key enabling technologies)
- TRL 6 – technology demonstrated in relevant environment (industrially relevant environment in the case of key enabling technologies)
- TRL 7 – system prototype demonstration in operational environment
- TRL 8 – system complete and qualified
- TRL 9 – actual system proven in operational environment (competitive manufacturing in the case of key enabling technologies; or in space)

Table 1. Technology Readiness Levels as defined in H2020

2 See http://www.acmedsci.ac.uk/policy/policy-projects/team-science/

3 Not all calls under SC and IL specify TRL levels. Nor does FET, which is aimed at technological research where applications are anticipated and known, and beyond the level of development covered in our definition of discovery research.

It is obvious that for a specific technology to reach the higher TRLs, it needs to build on research at the lower TRLs. Currently the partitioning of the funding of both Industrial Leadership and Societal Challenges is very much skewed towards the higher TRLs. This is exemplified by an analysis of the H2020 work programmes 2014-2015 and 2016-2017[4], in which we counted the frequency with which each TRL is assigned to calls (Figure 1). It is obvious that the lower TRLs are significantly underrepresented. Interestingly, and perhaps unexpectedly, the Societal Challenges calls on average seem to require higher TRLs than those of Industrial Leadership.

Even though the use of TRL nomenclature is not widely spread, these observations are in line with observations made on a more global scale when examining the distribution of Gross Expenditures on Research and Development (GERD). In general two-thirds of GERD is financed by the private sector, and one can safely assume that this corresponds to the higher TRLs. Of the one-third that is publically funded, at least 50% again is in the higher TRLs, leaving at most 20% for the lower TRL levels. Following another approach, GERD can be divided into basic research, applied research, and experimental development. Historic numbers (UNESCO, 2011) demonstrate that, for instance, the UK spends only 9% of the GERD on basic research, Japan 11%, US 17%, France 25%, Switzerland 27%. This implies that far less than 30% of the total GERD is spent on basic research, corresponding to the lowest TRL levels.

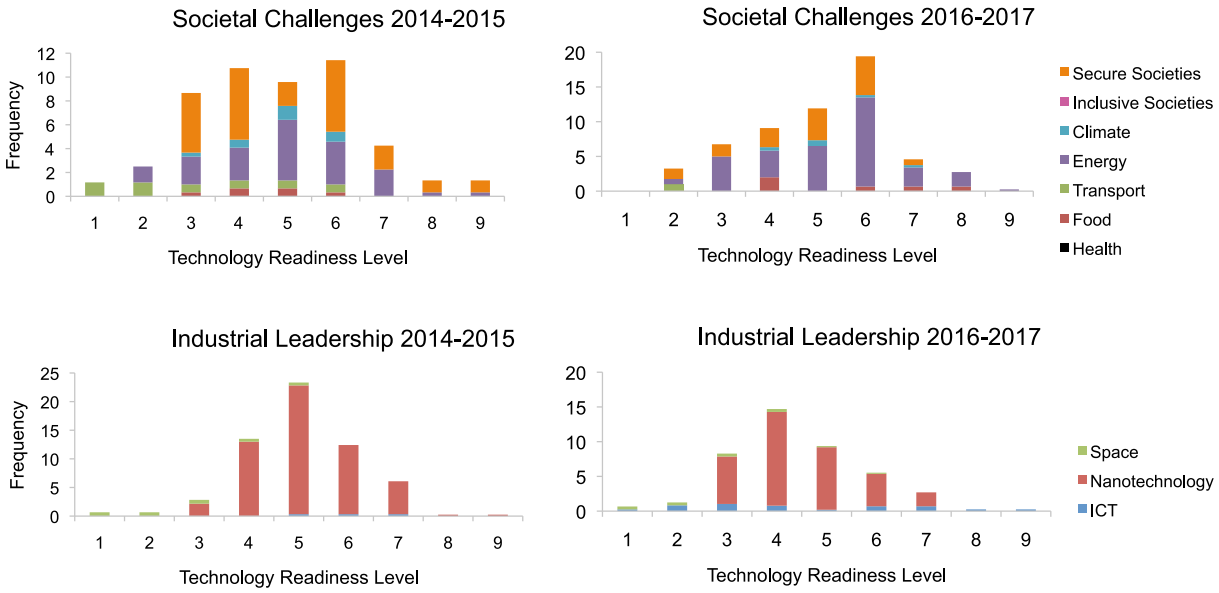

Figure 1: Use of Technology Readiness Levels in H2020 work programmes 2014-2015 and 2016-2017. To determine the distribution of Technology Readiness Levels (TRLs) over the different parts of H2020, we counted the frequency of each TRL in the 2014-15 and 2016-17 work programmes of H2020 (downloaded from the H2020 participant portal). Some specifics on the methodology: (i) We only included calls that were labeled *Research and innovation action or Innovation action* and excluded calls directed at small and medium-size enterprises *(SME)* and calls with the label *Coordination and support action* (CSA) or *Pre-Commercial Procurement* (PCP); (ii) We only included calls in which a TRL was explicitly mentioned; (iii) If one call listed a range of TRLs (e.g. TRL 4-6) we adjusted the weight accordingly; (iv) Some calls listed the TRL that should be achieved through the research project rather than the TRL at the start of the project. If a call listed the TRL as "development up to TRL X", we counted this as TRL X-1.

4 http://ec.europa.eu/programmes/horizon2020/en/news/horizon-2020-work-programme-2016-2017-published

The natural consequence of this bias towards higher TRLs is that a very large fraction of research that is not yet on a technology track is explicitly excluded, regardless of its potential societal or technological relevance or impact. This creates the risk that the pipeline of radically new ideas and concepts, which are so crucial for innovations and technological advances, will run dry. Therefore, in addition to the current approach where top-down and government-led research is heavily supported in many European countries, there should be sufficient room for bottom-up, investigator-driven, discovery research. In the next section we illustrate this point with a few current topics in the natural sciences.

Examples of collaborative discovery research in the natural sciences

In this section we illustrate the operation of and opportunities for collaborative discovery research in the natural sciences by exemplifying four current topics - from novel energy sources, to model systems in biology and health sciences, to nanophotonics for new optical devices and to big data. This selection by no means pretends to be comprehensive or directional, but merely wishes to illustrate the case with representative examples from the natural sciences. Similar cases could be identified across all scientific disciplines.

The examples all have in common that the design of the research projects involved do not anticipate any specific outcome from the onset. The main motivation always is to further knowledge in a (sub-)discipline, to gain deeper insight in fundamental laws of science, and to perlustrate unexplored territory. In some cases the outcome may be incremental only, but if new discoveries are made, impact and relevance will be very high.

1. Novel energy sources

Scientists have realised decades ago that the use of fossil fuel (oil, gas and coal) is not sustainable in the long run, due to depletion of the fossil energy reserves and the global warming caused by the use of fossil fuel through the emission of greenhouse gases. Many alternatives have been developed, such as biofuels (bioethanol, algae, bacteria…), solar energy and wind energy. All of these alternatives are currently at different stages of technological development and application. The current H2020 work programme aims at scaling up new and promising technologies that are currently at the laboratory scale (TRL 3-4) to “form the backbone of the energy system by 2030 and 2050”. However, opportunities for the type of research that will provide radically new insights and thereby lay the foundation for the energy system of the second half of this century are very rare. In the field of solar energy, appearance of new systems will be based on new chemical components and/or elaboration processes, i.e. new basic research results.

2. Model systems in biology and health sciences

The global ageing of the European population is a novel large-scale challenge which, as described in H2020, requires “a better understanding of the causes of health and disease, and making best use of big data, to develop better diagnostics, therapies, health promotion and disease prevention strategies at the personal and population levels, as well as technologies to support healthy ageing”. Decades of research have shown that most human diseases or pathological processes linked to ageing cannot be understood solely from research performed on

patients, especially when mechanisms have to be deciphered. For research into the basic mechanisms of health and disease we need alternative model systems like yeast, worms, fruit flies, zebrafish, mice, and others (including plants). There are three main strengths of using model systems in life science research:

(i) Model organisms can be used to identify mechanisms that are common to all living organisms such as normal and abnormal cell growth. Indeed every model organism has specific advantages in terms of manipulations, shorter life cycle, high sensitivity to mutagenic substances, simpler genetic setup, etc. Key concepts discovered in model organisms are not only relevant to human biology and medicine, but also to environmental biology, where they contribute to a better understanding of the interactions between live organisms and their environment.
(ii) Model organisms can be used to carry out systematic large scale genetic and/or pharmacological screens, which would be impossible to perform in mammals. These screens are used to characterise signaling cascades that regulate key biological processes and to identify novel candidate therapeutic agents. The systematic large scale approaches in model organisms are essential for research in biochemistry, genetics and pharmaceutical sciences, providing a basis for the advancement of medicine.
(iii) Some organisms possess specific proteins or other molecules that provide novel tools for experimentation. One of the best examples is the Green Fluorescent Protein (GFP), which is produced by a jellyfish, but can be used in other organisms to follow the behaviour of cells in a live tissue.

Thus, research using model organisms that are evolutionarily distant from humans is crucial for the detailed understanding of life processes, and therefore essential for the better understanding of the causes of health and disease. In a typical interdisciplinary collaborative research approach, scientists investigate both the basic and clinical aspects of genetic and environmental determinants of ageing, thanks to fruitful iterative exchanges with clinicians.

3. Nanophotonics for new optical devices

The discovery, in 1998, of the transmission of light through sub-wavelength apertures illustrates the unpredictability of applications arising from a breakthrough in basic science research (Ebbesen, 1998). The discovery soon led to abundant industrial applications in different fields from the improvement of lasers, to the observation of individual molecules in chemistry and to the development of spectroscopic sensors for biomedical applications. The cited experiment by Ebbesen and colleagues established new physical laws that were a priori completely unexpected and led to crucial improvements in the field of photonics. The fundamental breakthrough in this area was awarded the 2014 Kavli prize in nanoscience. This example shows how a basic science discovery has the potential to create a stronger impact, acting as a trigger for change and radicalisation of how technology problems are addressed. Still now, it is not at all defined where this discovery eventually will lead to.

4. Big data

In the 1930s, well before the invention of the computer, a group of theoreticians developed the statistical methods that today permit the analysis of large data fluxes (big data). In the near future, our society will face even greater amounts of information generated by everyday objects (embedded internet), trade, stock exchange, etc. At the same time, science is brought to study more complex systems: the human body in its entirety, earth atmosphere, macroeconomics, environment, etc. Mathematicians, theoretical physicists and computer scientists are currently

working to generate new ideas and to devise new paradigms in the field of discrete mathematics, Markov processes, random matrices, and artificial intelligence that could revolutionise the way we treat massive and complex information. These methods eventually will lead to a better understanding of the logic or the universal behaviour hidden under seemingly chaotic evolution of complex systems like the human brain, biological systems or social interactions. They also aim to optimise the accuracy and reliability of the relevant information extracted from large data sets.

Conclusions and recommendations

LERU is convinced there should be more room for bottom-up knowledge development in the collaborative part of H2020 (pillars II and III), fostering important links not only between university research laboratories but also out to industry. It is essential that the research laboratories of major European companies have the opportunity to collaborate with world-leading discovery research laboratories in the leading European research universities. To implement this, the existing, solid architecture of H2020 does not require major changes. Yet, we do propose one simple measure which could be implemented on the short term: **a more balanced distribution of TRL assignments to the various calls in the work programme 2018-19, in particular for Societal Challenges but also for Industrial Leadership**. The inclusion of low TRL calls (TRL 1 to 3) will allow Europe to harness the full breadth of its scientific excellence in order to contribute to solutions for both the short-term and long-term challenges of society.

Furthermore, the TRL framework, originally developed by NASA in the context of space industry and early-on adopted by military industries, suffers from major deficiencies in grasping all essential steps in translations from scientific breakthroughs and discoveries towards innovation. This framework reduces the research, development, and innovation process to a linear pipeline. Alternative views nowadays value much more the importance of open and more circular descriptions of the process, including the importance of multiple contributing technologies and feedback at various stages of the innovation chain (EARTO, 2014). **It is important to recognise that the limitations of the TRL nomenclature can skew scientific projects towards short-term applications and fail to recognise setbacks in technology maturity or appreciate new emerging technologies.**

In the longer term, LERU would like to see **new approaches for future EC research programmes to better target collaborative discovery research creating opportunities across universities and industry, in the context of pillars II and III of H2020, that does NOT focus primarily on shorter-term goals. The programmes should also specifically target higher-risk, potentially paradigm shifting science**, thus revolutionising domains where high relevance and impact is to be expected. LERU is convinced this would inspire *"the cutting-edge science, unconventional collaborations or new research and innovation practice"* the European Commission is aiming for. In the face of global competition for research talent and resources, there are great benefits to be reaped from Europe investing in collaborative, transdisciplinary and trans-sectoral discovery research to produce scientific breakthroughs and paradigm shifts. Coupled with better and more open mechanisms encouraging industry to exploit the results, this will lead to more innovative outcomes.

Finally, we also **call on national funding agencies to acknowledge the utmost importance of a balanced distribution of funding for research spanning the broad range of activities that have all contributed to the progress in science in the past**. The continuum of research activities should never be disrupted, certainly not by ignoring the importance of new discoveries, sometimes occurring serendipitously, but always based on research striving to solve important scientific questions.

Appendix

Discovery research and knowledge transfer in all directions: a short scientific history of MRI, mobile phones, scanning probe microscopes and monoclonal antibodies.

Magnetic resonance imaging

As with many inventions that are currently transformed into every day technology, it is almost impossible to reconstruct the line of discoveries that finally resulted in this medical diagnostic workhorse of modern health care: magnetic resonance imaging. Crucial initial ingredients are the description of magnetism and magnetic fields, the concept of radio waves, and the development of quantum physics, all areas in physics where many great minds were involved.

Nuclear magnetic resonance (NMR) was first described and measured in molecular beams by Isidor I. Rabi in the late 1930s, when he used the absorption properties of radio waves by atomic nuclei to reveal the magnetic properties for different isotopes of the same element. This earned Rabi the Nobel Prize in Physics in 1944, and the technique is still used in nuclear structure research of exotic nuclei at large facilities like CERN. Rabi's experiments extended the technique of the Stern-Gerlach experiment, which was critical in establishing quantum mechanics as the way to describe the atomic world. In 1946, Felix Bloch and Edward Mills Purcell expanded NMR for use on liquids and solids, for which they shared the Nobel Prize in Physics in 1952, thus creating a universal tool for understanding the structural information of essentially all materials with atomic precision.

The realisation, in the 1970s, that the chemical environment of protons is very different for different tissues and organs in the human body would allow detailed imaging using NMR techniques. Paul Lauterbur developed experimental techniques that allowed rapid acquisition of two dimensional images, using magnetic field gradients. And Peter Mansfield was credited with introducing the mathematical formalism and developing techniques for efficient gradient utilisation and fast imaging reducing the time to generate magnetic resonance imaging (MRI) scans by orders of magnitudes. They shared the Nobel Prize for Medicine in 2003 (Lauterbur, 2003).

Many others have contributed to the development of NMR and MRI techniques. This includes Johann Radon, a pure mathematician interested in furthering knowledge in analysis and geometry, who introduced in 1917 a transform upon which current tomography techniques are based. And there are the Nobel laureates in Chemistry, Richard R. Ernst (1991) and Kurt Wüthrich (2002), honoured for their contributions to the development of high resolution NMR spectroscopy, and in biological macromolecules in solution, respectively.

No doubt, MRI, as a technique that now saves lives every day, builds on an impressive range of discovery and knowledge that was obtained in the curiosity-driven process of furthering the understanding of scientific questions posed in contexts that by no means were related to the application that now is at hand. And once the high potential of these concepts was realised, decades of targeted research finally led to this indispensable tool in modern health care.

The mobile phone

Our society is witnessing the vast and impressive progress that results from research and development in the phone industries since the first mobile phone call took place in Helsinki in 1991. While at that time mobile telecommunication involved slow-performing, brick-sized devices, the current capabilities of smart phones are truly impressive. No doubt this evolution has profited from targeted investments in directional research. But by the time the telecom industry could deliver the first operating mobile phone, almost two centuries of discoveries in physics, mathematics, and information science had passed, as illustrated in Figure 2 below, from Neuvo (2008).

The fundamentals of electromagnetism and electromagnetic waves were discovered and explored in the 19th century by such pioneering physicists as Morse, Faraday, Maxwell, Bell and Hertz. The same era produced ground-breaking mathematical concepts such as Fourier analysis, Poisson processes, Galois fields and Markov chains, all known and applied in numerous and diverse technological fields. Scientific and technological evolutions of the early- and mid-20th century started to integrate these concepts into information sciences, and with the advent of the transistor and the subsequent developments in microelectronics, along with the (r)evolutions in information theory and digitalisation, the age of the digital cellular systems started. None of the early scientific pioneers had in mind the mobile wireless society that currently is ours.

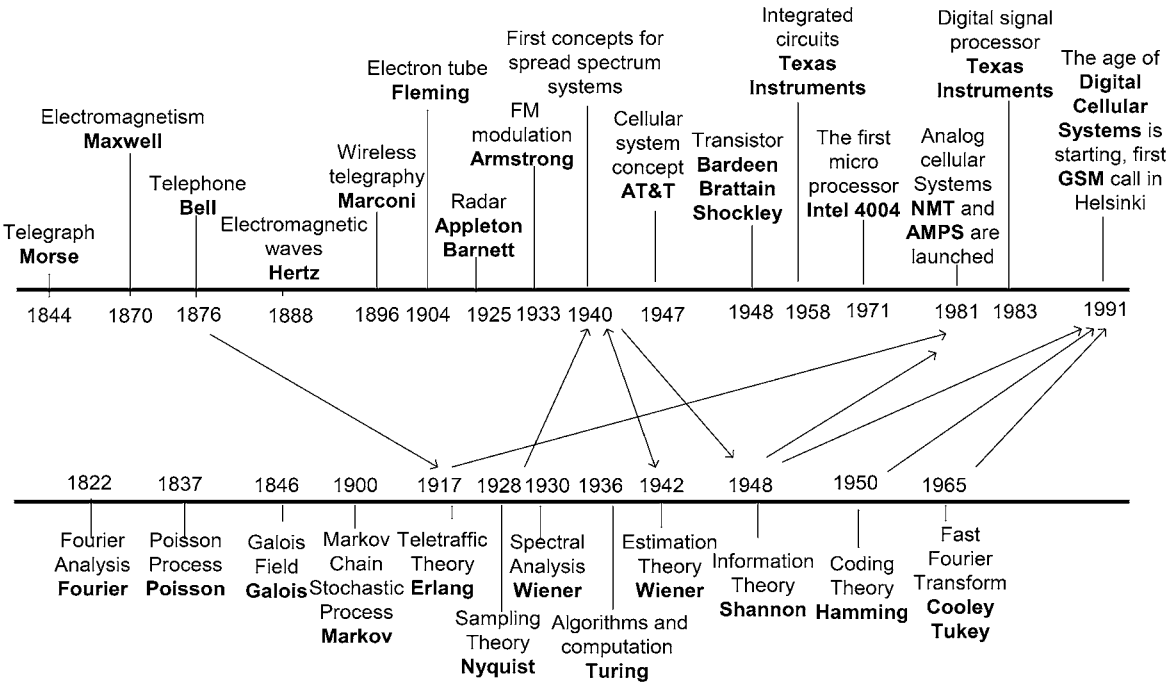

Figure 2: Inventions of the past that gradually paved the way towards mobile telecommunication. The top time line describes evolutions in physics, while the bottom is on mathematics and information sciences (Neuvo, 2008).

Scanning probe microscopes

The development of scanning tunneling microscopy (STM), along with atomic force microscopy (AFM), opened up the area of nanotechnology. It is a high-impact example of collaborative work that has its basis in fundamental physical phenomena, developed across both industrial and university research laboratories.

The development of STM techniques allowed surfaces to be imaged at the atomic level and for the first time created the possibility to directly manipulate nanoscale objects. This enabled the opportunity to build new nanoscale structures, such as nanowires. The development of STM, in 1981, was recognised with the 1986 Nobel Prize in Physics going to its inventors, Gerd Binnig and Heinrich Rohrer[5]. The beauty of the development is that both Binning and Rohrer had no background in microscopy techniques or surface science, but brought their fundamental knowledge of quantum tunneling in superconductivity and of the basic areas of phase transitions and critical phenomena. The development of STM occurred under the auspices of the IBM research laboratories in Zurich. Whilst Binning and Rohrer clearly demonstrated the feasibility of such an experimental approach, in order to unleash the full potential of this technique, a comprehensive microscopic theory had to be applied to be able to thoroughly analyse the results. Much of this pioneering work occurred in close collaboration with industrial research laboratories and universities.

The basic concept underpinning STM is quantum tunneling. This is when wave-particle duality allows a particle, such as an electron, to tunnel through a (energy) barrier it could not cross in classical mechanics. The same phenomenon also plays a key role in computers' flash drives. STM works by scanning a conducting probe across the surface of a material. The probe carries an electrical current which tunnels across the gap between the microscope and the material. By measuring the current one can measure whether the gap (strictly speaking the local density of states) is becoming greater or smaller and hence reveal a detailed image of the surface. This also highlights a limitation of STM in that it requires electrically conductive materials to operate.

The limitations of STM prompted the invention of the AFM, by Calvin Quate, Christoph Gerber and Binnig. Again the work was undertaken across both industrial and university research laboratories, with Binning and Quate associated with Stanford University. AFM is now at the forefront of exploration at the nanoscale and is a tool that has moved beyond the study of surface physics. AFM is widely available commercially and has opened up the exploration of the mechanical properties of cells and tissue as well as the study of pathogen-drug interactions.

5 http://www.nobelprize.org/nobel_prizes/physics/laureates/1986/

Monoclonal antibodies

In 1975 two scientists at Cambridge University, César Milstein and Georges Köhler, isolated and reproduced the monoclonal antibodies that defend bodies against foreign invaders. Now, monoclonal antibodies account for a third of all new pharmaceutical treatments, and the market for monoclonal antibody drugs is nowadays worth an estimated 30 billion euro. In 1984 they were awarded the Nobel Prize in Physiology or Medicine together with Niels K. Jerne for "theories concerning the specificity in development and control of the immune system and the discovery of the principle for production of monoclonal antibodies"[6].

Antibodies are large proteins produced by immune cells in reaction to foreign substances such as viruses, bacteria or large molecules (antigens). The antibody is able to recognise and bind to a part of the antigen, thus assisting other parts of the immune system in detecting and neutralising it. Monoclonal antibodies are very well suited for therapeutic purposes, e.g., in cancer: monoclonal antibodies designed to recognise proteins on the surface of tumor cells can prevent cell growth, stimulate cell death or promote recognition of the tumor cell by the immune system (immunotherapy).

In the 1970s Milstein and Köhler studied the structure of antibodies and the mechanism that generates antibody diversity, fundamental immunological research building on the work of many earlier scientists. During their studies they developed the so-called hybridoma technique, which makes it possible to produce monoclonal antibodies against any given antigen in the laboratory. Even though the clinical relevance of their finding was clear almost immediately, there were still serious hurdles to overcome. For example, because the monoclonal antibodies were produced by mouse immune cells, they caused severe side effects in humans. Major research efforts in the 1980s and 90s were put into optimising monoclonal antibodies for therapeutic use, resulting in a large and rapidly growing number of therapeutic antibodies on the market today, used not only in oncology, but also to treat autoimmune and inflammatory diseases like rheumatoid arthritis, multiple sclerosis and psoriasis.

Besides their therapeutic use, monoclonal antibodies have also become an indispensable tool in molecular biology research. Because they bind specifically to one given molecule, monoclonal antibodies can be used to detect or purify this molecule. Techniques to study the presence of specific proteins in fixed tissue sections, like immunohistochemistry or immunofluorescence, would not have been possible without the seminal discovery by Milstein and Köhler.

6 http://www.nobelprize.org/nobel_prizes/medicine/laureates/1984/

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About the authors

This note was written by Peter Lievens (KU Leuven), Brigitte Galliot (Université de Genève), Floor Frederiks (Universiteit Leiden), Jean-Marc Planeix (University of Strasbourg), Nick Brook (University College London), Katrien Maes (LERU) and Geert de Snoo (Universiteit Leiden). Input was provided by Karen Maex (University of Amsterdam), Pere Lluís Cabot Julia (Universitat de Barcelona), Athene Donald (University of Cambridge), Andrew Mount (University of Edinburgh), Andres Jäschke (Universität Heidelberg), Jouko Väänänen (University of Helsinki), Stijn Delauré (KU Leuven), Tom Welton (Imperial College London), Olov Sterner (Lund University), Pierre Désesquelles (Université Paris-Sud), Gerrit van Meer (Utrecht University), Maria Hijman (Utrecht University) and Michael Schaepman (University of Zurich). The note is based on discussions within the LERU Working Group of Deans of Natural Sciences. LERU is grateful to them and to the LERU Policy Committee, Vice-Rectors Research, EU Project Managers and the Rectors' Assembly for their valuable feedback.

LERU Office

Minderbroedersstraat 8
B-3000 Leuven
Belgium

tel +32 16 32 99 71
info@leru.org
www.leru.org

@LERUnews