



Thirty years of European biotechnology programmes: from biomolecular engineering to the bioeconomy

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This article is dedicated to the memory of Dreux de Nettancourt (1933–2011), first Head of Division of Biotechnology at the Directorate General Research of the European Commission.

This article traces back thirty years of biotechnology research sponsored by the European Union (EU). It outlines the crucial role played by De Nettancourt, Goffeau and Van Hoeck to promote and prepare the first European programme on biotechnology (1982–1986) run by the European Commission. Following this first biotechnology programme, others followed until the current one, part of the seventh Framework Programme for Research, Technological Development and Demonstration (2007–2013) (FP7). Particular attention is given to the statutory role of the European institutions in the design and orientation of the successive biotechnology programmes, compared to the more informal – yet visionary – role of key individuals upstream to any legislative decision. Examples of success stories and of the role of the biotechnology programmes in addressing societal issues and industrial competitiveness are also presented. Finally, an outline of Horizon 2020, the successor of FP7, is described, together with the role of biotechnology in building the bioeconomy.

The birth of European research programmes in biotechnology

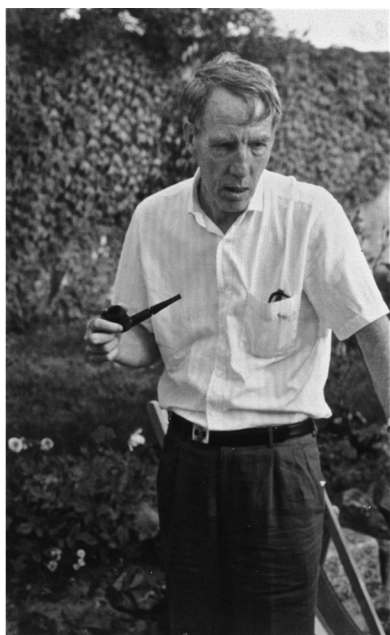
This article outlines some of the most important highlights of the past 30 years of EU biotechnology research, putting particular emphasis on the political context that led to the birth of the EU biotechnology programmes and on the evolution that biotechnology followed during this period. The authors acknowledge that their personal involvement in the conception, implementation and management of different EU biotechnology programmes has certainly influenced them, thus introducing

a degree of subjectivity in the way the summary of these 30 years of EU Biotechnology is addressed in this publication. Although maximum care has been taken to check the information presented with original documents and publications, it is not entirely excluded that certain omissions, maybe errors as well, might be left involuntarily in the text. This article is, however, not intended to be a comprehensive history of EU biotechnology as a whole, but rather an outline, animated by real life testimonies, of the most important milestones during this period.

☆ The views expressed in this publication are the sole responsibility of the authors and do not necessarily reflect the views of the European Commission or its Directorate General for Research and Innovation.

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Dreux de Nettancourt, Head of the Biotechnology Division at the European Commission at the time of the Biomolecular Engineering Programme (BEP)

The very first notion of mobilising public funding at European level for biotechnological research crystallised within the offices of the European Commission in 1975. At that time, three senior scientific officers of the Research Directorate General had the initiative to address their authorities with a visionary report on the potentials of modern biology. Their names should therefore never be forgotten, and this must be the place to give full credit to their catalytic and decisive role in science policy-making for Europe. They are: Dreux de Nettancourt, André Goffeau and Fernand van Hoeck [1].

Why was this period in time so crucial?

The question of time is a relevant one on both scientific and political scenes. The mid-1970s, for scientific minds, just came after two successive periods of change: one of discovery and the other of questioning. Each built an undeniable pressure on those involved in science monitoring and policy design. It needs to be recalled that a couple of decades only had elapsed since major discoveries had been made, which any informed observer would describe as having the potential to revolutionise the understanding of living beings and of their complex properties. In 1953, Watson and Crick unravelled the double helix structure of the DNA molecule [2], while in 1961, Monod and Jacob elucidated the regulation of protein synthesis [3]. In 1962, Arber discovered bacterial restriction enzymes having the capacity to dissect the DNA molecule in an entirely predictable way [4]. And in 1969, a 'gene', in other words a theoretical concept hypothesised from experimental evidence over about a century, was isolated from a bacterium in its molecular form for the first time by Shapiro *et al.* [5]. The authors of this report, like most of their peers, had to deliberate over this accumulation of paradigm-changing discoveries about the most intimate functioning of living beings.

A second period, full of questioning followed closely in the wake of the first, one which proved to be very much contextual to policy

work inside European institutions. It corresponded to the early 1970s, during which time scientific elites all over the world were addressing the responsibilities of researchers in molecular and cellular biology and the potential for fully mastering the most vital processes involved in the replication of life itself and, ultimately, the generation of new living forms. This was a rather frenzied period, stretching from 1970 and a conference on 'The social impact of modern biology' under the auspices of the British Society for Social Responsibility in Science, through the 1974 Paul Berg initiative for a voluntary two-year moratorium on recombinant DNA research, to the 1975 Asilomar Conference that put forward guidelines for regulating recombinant DNA research. These could all be seen as unilateral initiatives of scientists or science-funding agencies, sometimes with the support of their governments, to raise fundamental societal issues, notably those speculating on risks associated with the application of recombinant DNA technology. However, they all took place in rather closed and specialist circles.

De Nettancourt, Goffeau and van Hoeck were, thus, building their case for a European research initiative at the intersection of a knowledge revolution-in-the-making on the one side and, on the other, a truncated debate which proved sufficient to alert investors and politicians in part of the developed world, but missed an opportunity to seriously inform public opinion. The Member States of, at that time, the European Economic Communities (EEC) in 1975 were, as a matter of fact, still poorly organised in this novel field, with the possible exception of the UK which had just joined the EEC in 1973.

The relevance of the timing also relates to the reality of the political climate in Europe. In 1975, there was no such a thing as a 'research and innovation policy' for the EC. Put simply, research was not yet formally recognised as a Community competence as the Common Agricultural Policy (CAP) was. References to research existed marginally in the Coal and Steel Treaty as well as in the EURATOM Treaty. Under those treaties, budgetary appropriations were foreseen for ancillary research activities. Under the Treaty of Rome however, assuming a political momentum had existed, the only way to invite Community research was to invoke an Article stipulating that the Commission would be justified to put forward *ad hoc* initiatives when necessary, if other chapters of the Treaty did not provide adequate provisions. This timid opening had actually been the starting point for small medical research and agricultural research programmes during the sixties and seventies, which excluded direct funding and limited the intervention of the Commission to coordinate relevant national research work.

One key remark ought to be made right away, before enumerating the steps taken to develop a new programme. The Cold War was having a visible impact, in particular in relation to public support to science and technology and, most explicitly, on modern biology. The efforts of the Soviet Bloc to master technological advances were mirrored in Western Europe, with the overt support of the USA, to capture the best brains on the west of the Iron Curtain. This was the origin of international treaties and conventions, for example, to establish CERN (Organisation européenne sur la recherche nucléaire) in Geneva on particle physics, EMBL (European Molecular Biology Laboratory) in Heidelberg around molecular biology and EMBO (European Molecular Biology Organisation). It also gave rise to NATO (North Atlantic Treaty Organisation) scientific fellowships and was influential in designing the

EURATOM Treaty as well as allowing the creation of a multi-site Joint Research Centre for the EC. These developments took place with a view to developing peaceful and safe uses of nuclear power and, in some way, there was much more EC money readily available through the EURATOM Radiation Protection Programme for European collaborative research in biology than could have been expected at that time under the Rome Treaty.

What steps led to the development of a new programme?

An internal EC report from De Nettancourt *et al.* (1977) [1] led, after six years of difficult negotiations, to the 'Biomolecular Engineering Programme, (BEP)' (1982–1986), with its initial appropriation of seven million ECU (the precursor of the Euro). The European Institutions and Member States had received the Commission proposal based on the Treaty of Rome, and had been trying to come to an agreement on the scope, budget and operational rules of the programme within the embarrassing context that no similar programme existed under any of the participating national governments.

During the drafting phase, and to flesh out the technical content and emphasise a European added value beyond on-going national research, the authors of the internal EC report built their case on invited studies, commissioned from leading scientists at the cutting edge of biotechnological advances [6–9].

At the same time, Europe stepped into a worldwide debate on societal aspects of modern biology. Three relevant developments were crucial. Firstly, the adoption in 1978 of the FAST programme (Forecasting and Assessments in the field of Science and Technology) for the EC, including a sub-programme on 'the Biosociety' which considered potential impacts with a time span extending over the following 30 years. Secondly, the first regulatory measure, adopted for the EC with regard to potential large-scale implications of biotechnology, namely a directive concerning 'safety measures against conjectural risks associated with work on recombinant DNA' [10]. Finally, the inter-institutional symposium, under the auspices of the Economic and Social Committee of the EC, inviting debate on 'Genetic Engineering' [11].

The Biomolecular Engineering Programme (BEP) was launched in 1982 and driven by a deliberate technology push, maybe naïve but in tune with the formidable new methods used by bench scientists working with living organisms. The BEP was initially built around two main areas, namely second generation bioreactors, and genetic engineering for agriculture and the agro-food industry. The reason for such a narrow scope was due firstly to the limited funding available and secondly because, at that time Member States were of the view that health related biotechnology would have to remain an exclusive remit of academic institutions and industries with a strong national base. In addition, more than two-thirds of the overall EC budget went on financing the CAP and, hence, an obvious driver for research benefitting agriculture. As the Treaty of Rome did not yet define any specific mandate for EC research, a precautionary wording restricted the eligibility of funding to the so-called 'pre-competitive' domain. The wording is legally binding but, at the same time, equivocal in different linguistic versions. The pre-competitive criterion may have acted like a warning, but in two different directions. Initially, it was the most orthodox interpretation to admit that research funded through BEP should never be seen as competitive. 'Pre-competitive' simply meant non-competitive. As this small

programme proceeded, other voices started to argue that 'pre-competitive' also meant a condition that just precedes the conversion to competitiveness, or in a more informal way that 'pre-competitive research' is where industrial competitors feel able to collaborate. These different interpretations rapidly disappeared as soon as comprehensive Framework Programmes became established from the mid-1980s, and an explicit justification for EC research was introduced in the Treaties, starting with the Single European Act. At this point in time, EC research became invited with the specific purpose 'to strengthen the scientific and technological basis of European industry and to encourage it to become more competitive at international level' [12].

In retrospect, it is evident that the timing of the BEP had an impact on maturing the ideas for the first comprehensive Framework Programme for all EC-sponsored research and technological development, into the then fragmented and scattered research funding climate. In particular, this small programme opened the era of technology-driven initiatives, capable of breaking through the academic boundaries of more traditional disciplines. It also became the place for designing ambitious proposal evaluation procedures, based on independent international peer review, under the scrutiny of a programme committee composed of representatives of the Member States. Last but not least, the programme hosted in those early days a training scheme parallel to project funding, which convincingly pointed to the vital need to boost scientific mobility across frontiers as a mechanism fostering excellence. In a sense, the BEP can claim – together with information technology programmes renamed in the meantime 'Esprit' – to be the prototype think-tank and test bench for the structure and operational rules of the newly designed, all encompassing, Framework Programme.

Least documented, however most decisive: the human factor!

In the story of the BEP, the human chapter is quite elusive but is so essential that it deserves to be examined. The memory kept of these early days may be fragmentary, the appearance of key figures may now look anecdotal, and yet it remains a strong belief that nothing could have been more decisive than the coming together in a crucial moment of few visionary individuals. Two anecdotes serve to illustrate our story.

The first one exactly reflects a famous statement in a book by Thierry Gaudin [13], which says: "Creation usually (1) sparks from displaced persons, and (2) results from their listening capacity".

Displaced persons? Well, De Nettancourt was a French gentleman with some Irish blood, born in Morocco, who studied in the USA and in Canada, started his career in the Netherlands and moved to Italy, before joining the European Commission in Brussels.

Listening capacity? A previous paragraph explained the reason why much of the EC funded research in biology until the late seventies came under the EURATOM flag and, mainly, as a part of the Radiation Protection programme. Now this programme was financially supporting, around the time that a future BEP was being developed, several pan-European working groups of biochemists, cell and molecular biologists, active in the elucidation of DNA damage and repair mechanisms. This was the time when numerous DNA enzymes (DNA polymerases, DNA glycosylases, DNA ligases) were isolated and characterised from several living organisms, with a view to completing the picture of DNA metabolism under different physiological or stressed conditions.

Whereas virologists and microbiologists worldwide were effectively at the front line of the discoveries from which recombinant DNA technology could lend itself to revisiting basic biological mechanisms, no doubt that the intellectual climate of prokaryotic/eukaryotic enzymologists and radiobiologists surrounding EC offices gave, as BEP was still in its drafting phase, a somewhat peculiar inclination to the early design of the envisioned European cooperation. In other words, if BEP can now be designated as being the cradle of a whole lineage of EC biotechnology programmes, the Radiation Protection Programme in those days could well be considered the cradle of BEP. European collaboration was already lending itself to the magic of serendipity!

Our second anecdote involves actors who were external to the EC administration, being recognised and prominent scientific figures in their own countries. This gives us the opportunity to introduce the 'Programme Committee' composed of national delegations, and established by Council to oversee the EC programme management. Under the BEP programme, the Programme Committee was in the form of an 'Advisory Committee for Programme Management' (ACPM), before it became later a 'Committee of an Advisory Nature' (CAN) as called for under the subsequent Biotechnology Action Programme (BAP) (1985–1990) and BRIDGE programme (1990–1993). With forthcoming programmes and increased budget however, the Council would require that the Programme Committee be upgraded into a 'Regulatory Committee', thus no longer confined to giving an advice but taking part in the statutory decision making process by means of positive or negative opinions adopted by qualified majority. This became a shift in governance, the consequences of which, amplified by the gradual increase of the number of participating countries, have not been commented on enough. With the ACPM under the BEP, and nine Member States to deal with at the start and 12 at the end of the BEP, following first the accession of Greece and then of Portugal and Spain a few years later, the national delegations still recruited their members among top scientists familiar with science policy-making in their own countries. The tendency afterwards has been to configure these delegations with ministerial officials supported by representatives of science funding organisations, or more recently from Ministries of Industry or Economic Affairs. With regard to the Advisory Committees of the early days, whose composition included some splendid characters, the pursuit of superior aims and the gradual building of common intelligence were typically the most immediate triggers of delegates, whose curiosity and personal judgement had often taken the place of an official mandate. This expert profile, representing a 'nascent state', which probably now belongs to the past, is exemplified below under real conditions (Boxes 1 and 2).

Thierry Gaudin [13] goes on to qualify the 'nascent state' as an obligatory pathway to the deployment of novel initiatives. The BEP programme represents the nascent state of EC biotechnology programmes growing in importance, coverage and ambition. A few officials with relevant scientific credentials joined the EC administration later, supported and led by the European Commission to develop new programmes and policies. While developed in the same spirit, these new programmes and policies paid greater attention to creative environments, considered investment mechanisms in addition to traditional subsidies, adjusted to a mosaic of newly related national initiatives, and thus embarked

BOX 1

Juste retour (recovery) and juste détour (diversion)

André Berkaloﬀ was a member of the French delegation in the BEP-ACPM. He was a university professor (Paris-Orsay), author of a famous handbook on cellular biology & physiology used as a guide by a generation of students, president for a time of the scientific council of the INRA (French agricultural research institute). The event which made him famous in the context EC biotechnology had never been witnessed before. The EC Commission presented to the ACPM the shortlist of project proposals considered after evaluations as being eligible for funding. The committee was invited to provide its advice as usual. One has to remember that proposals did not need to include participants from different Member States (the transnationality criterion was only introduced within the rules as from 1985). Berkaloﬀ's attention was called by two proposals having to do with the molecular genetics of a pathogenic Gram positive bacterium infecting horticultural plants and referred to as *Erwinia*. The long term interest of these proposals was evident, having in mind that *Erwinia* operates a well described secretion apparatus, synthesises cellulases and pectinases of potential interest for industry, and had been already partly exploited for an asparaginase tested in cancer therapy, without even mentioning the demand of efficient strategies of disease control under agricultural conditions. Yet, 3 French laboratories (led by Kotoujansky, Robert-Baudouy and Chambost) managed to get a high mark which promoted them in a good position of the shortlist, while the Belgian laboratory with the best expertise in molecular biology (led by Toussaint) fell just below the cut-off point. The advice of the ACPM, as expected, had been for the Commission to find an amount of money just sufficient to rescue the Belgian proposal, and encourage thereafter all contributors to develop some form of cooperation. Regrettably, there was no money left and the Commission confessed being practically unable to follow the advice. This was the time when Berkaloﬀ stood up and argued that the benefit to European science and ultimately to the contributors themselves would be greater if these all got a reduced amount of money and still could join forces. To the general astonishment, he suggested to remove a reasonable amount from the funds attributed to the French part (his own country) and let the Belgian part go in, thanks to this money transfer. Very politically incorrect from the 'juste retour' (recovery) point of view, no doubt, but a wonderful coup of strategic inspiration from the 'juste détour' (diversion) point of view!

on what developed into a truly fascinating triple decade of science policy-making. Anything but trifling!

A comprehensive summary of BEP with its main achievements has been published elsewhere by Magnien [14]. For more details concerning the following BAP, BRIDGE and Biotech programmes, see references [15–18]. A more detailed historical perspective of the development of biotechnology, and in particular of the first ten years of EU programmes on biotechnology is presented by Cantley and de Nettancourt [19], Magnien and de Nettancourt [20], Aguilar [21], Magnien [22] and Goujon [23].

The consolidation of biotechnology programmes

Four other Biotechnology programmes came in sequence between 1984 (BEP) and 1998 (BIOTECH II). However, the 15 years had been anything but a linear progression. As a matter of fact, this period saw a succession of biotechnology programmes regularly reinforced in terms of budget and also periodically redesigned in

BOX 2

Magni's principle

Another character worth giving credit to could easily be Giovanni Magni, member of the Italian delegation under BAP/BRIDGE. He was another university professor (Pavia-Milano) having gained his reputation in yeast genetic research. Like Berkaloﬀ his predecessor, he also was able to stand up and provide sudden enlightenment. Here, we touch upon the very sensitive issue of prioritisation. The instrument of prioritisation in the EC Biotechnology programmes, like in any other EC programme, has been the yearly workprogramme listing specific objectives and tasks for the period, as well as corresponding funding modalities and budgetary breakdowns. Unwillingly, an indirect effect of the restoration of the regulatory nature of committees in 1992 with BIOTECH I and BIOTECH II programmes, along with the higher number of participating countries, had proved to render diﬃcult any exercise aiming at recognising harsh priorities, whatever the strategic reasoning could be to underpin such choices. Although still in an advisory capacity in the late eighties, the Committee Magni belonged to was already revealing the temptations of national delegations to include most of their pet subjects suggested all over the board, with representatives supporting each other until they got satisfaction. The Commission encountered real diﬃculties to maintain a clear managerial drive, and to ensure that any yearly workprogramme would contain just the set of priorities that would enable the programme to make visible difference under the time limitations. Here came Magni with a brilliant proposal to his fellow members. 'Let's make commitment that any delegation decided to push for an additional priority would only be listened to by this Committee if the same delegation was able to indicate which other priority could be removed in compensation, ensuring that such removal could still be supported by a majority of the members'. The initiative was so successful that the Commission continued to refer to it many years after the event, and gave it the unforgettable name of 'Magni's principle'.

their semantics and underlying policy objectives as they grew in both structure and objectives (see Fig. 1).

Content-wise, the programmes gradually included subjects in the fields of health, biosafety, environment and the industrial applications of biotechnology. Incrementally, from 'green biotechnology' in the BEP, a more balanced 'biotechnology rainbow' emerged over the years. This 'rainbow' referred to the colours assigned to different aspects of biotechnology: red (health biotechnology), green (plant and environmental biotechnology), blue (marine biotechnology) and white (industrial biotechnology). The representation of diverse national interests, and an attempt to achieve a reasonable matching between areas prioritised at Member State level with those appearing in the EC programme, together continued building pressure for work programmes that were forced to become more and more inclusive.

Subsidiarity to ensure an optimal EC added value – on top of the mere excellence of projects – had remained the dominant *modus operandi* for all decision-makers, however in an interestingly evolving way. Under the BEP, subsidiarity was achieved only partially by the decision to single out an entire sector (agriculture and food), while leaving Member States as the sole operators in other sectors. From the mid-1980s, however, the pursuit of subsidiarity in more-or-less all-encompassing programmes would require a careful differentiation process at the level of topics and tasks. To allow for such fine tuning, the national delegations in the respective

committees were put under repeated pressure to share with their other delegations and with the Commission information on their national efforts under each theme and topic. Hence, the delineation of EC priorities became a more rational process. Specific studies and compilations, even a dedicated *ad hoc* group of one of these committees, were called for. This exercise proved difficult to implement, incomplete and became rapidly obsolete. Clearly, this was signalling a serious limitation in trying to ensure an optimal governance of Biotechnology (or other research likewise) across Europe, if the shared information was only allowed to flow in a centrifugal mode (from the EC core to Member States), while the centripetal mode (from the Member States to the EC core) failed to feed the process. The governance issue was revisited in 2002 with the publication of the Commission Strategy for Life Sciences and Biotechnology [24] and in 2012 with the Commission Communication on the Bioeconomy [25]. It also became an issue in the wider context of new initiatives encouraging Joint Programmes with Member States in variable configurations [26] – but this is another story.

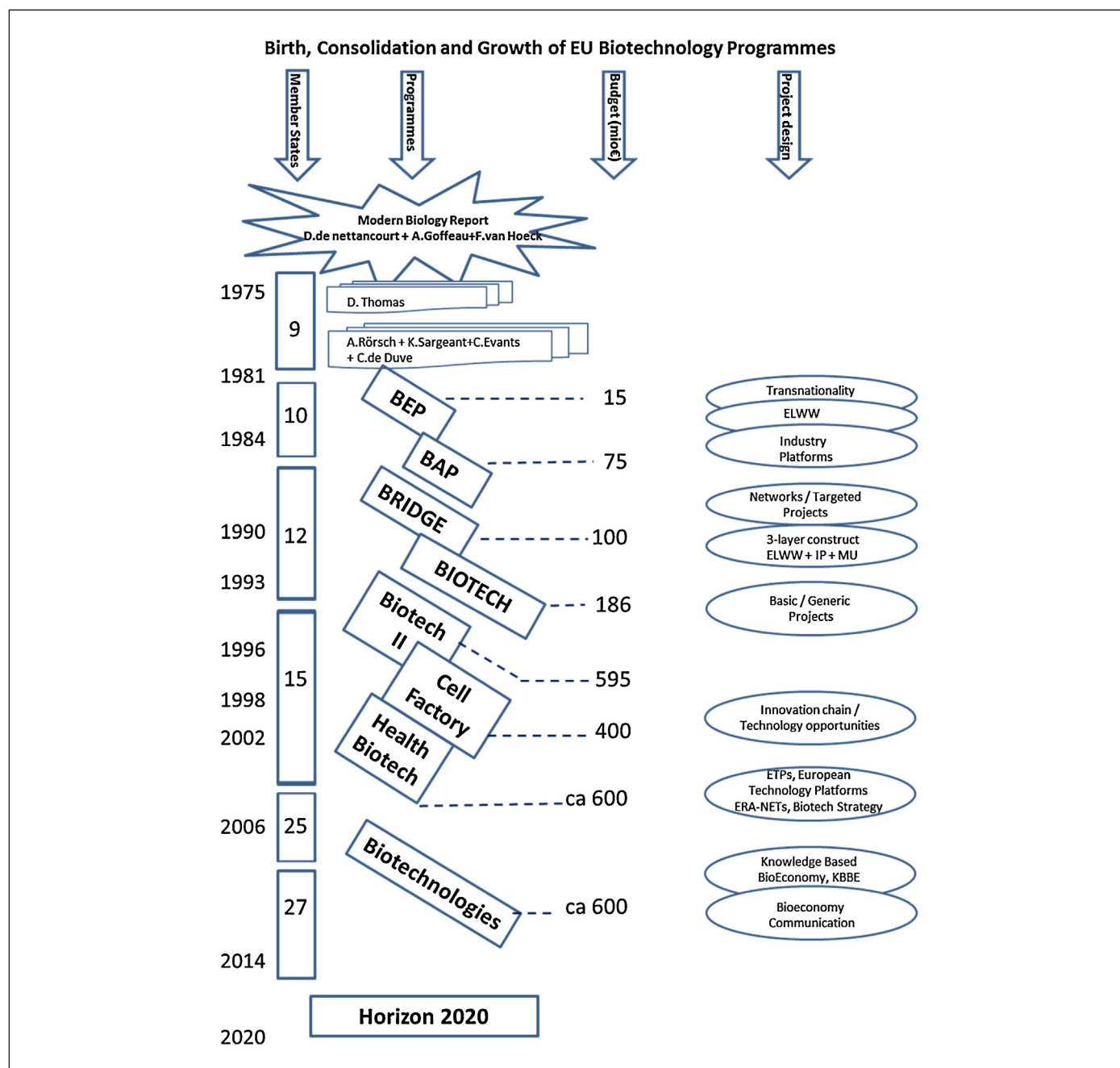
It should be recognised, however, that specific EC features of the content of biotechnology programmes have emerged during the period under discussion. These features result from the growing influence of the European Parliament, the sensitivity of policy-making to crisis prevention and management, and the evolving views of civil society.

Where can we see the signature of the European Parliament?

The Parliament probably achieved more in the field of biotechnology in its struggle with Council to introduce more democracy into decision making than in any other area. Among others the areas of safety assessments associated with GMOs (genetically modified organisms), microbial ecology, *in vitro* pharmaco-toxicology testing and – as cross-cutting issues – the promotion of the participation of SMEs (small and medium size enterprises) and the definition of an ethical approach to funding research, can be highlighted. The resulting impact has certainly been more perceptible towards the end of the sequence of programmes, during the nineties, and can be briefly summarised in the following terms:

- Safety assessments associated with GMOs
Since GMOs came onto the agenda, two different and complementary areas have received consideration: one to produce GMOs offering definite advantages while the other to control GMOs both in confinement and in the field. It is quite remarkable that, from the BAP to BIOTECH II, the level of funding which has gone into biosafety issues had been continually increasing in both relative and absolute terms, to the point that the EC has ended-up providing as much support to control methods as it does to production strategies. The credit for this can be laid squarely at the Parliament in its role of promoter of the precautionary principle.

- Microbial molecular ecology
It is by now well recognised that molecular microbiology, as part of the renewed biotechnological approaches to soil ecology, is radically changing our understanding of the invisible microbiota thriving below ground level, a unique reservoir of biodiversity. Traditional knowledge areas such as cell-to-cell communication, chemotaxis, antibiotics, plasmid instability, virulence, symbiosis, horizontal gene transfer, the species barrier, and many others have to be seen under completely new

**FIG. 1**

Birth, consolidation and growth of EU biotechnology programmes.

light since biotechnology started to pervade the field. This conceptual enrichment from soils viewed as substrates to soils viewed as fermenters and, one step further, to soils as microcosms of an on-going accelerated co-evolution of species, could not have been achieved without the advent of microbial molecular ecology as a new scientific discipline [27,28]. And such a discipline clearly penetrates academic environments with exceptional encouragement through (among other factors) the external pressure exercised by the European Parliament to monitor and strictly control field releases of GMOs. EC biotechnology programmes were in the right place and at the right moment to host these beneficial developments.

- *In vitro* pharmaco-toxicology testing

Behind testing methods lies the thorny issue of animal experimentation. The European Parliament proved to be, and still is, quite vocal to reflect the widely diverse citizens' concerns for animal rights. It largely disseminated the '3Rs' principle (Reduction-Refinement-Replacement) applicable to animal experiments for medical or scientific purposes. Hence, the high expectations placed on the potential of biotechnology as a means to realise the 3Rs, and the ambition of the Parliament to reinforce a research sector on '*in vitro* testing'. Such *in vitro* tests need developing to a stage where they can realistically fulfil the objective of bringing the number of

animals subject to experimentation to a reasonably low-level throughout the EU.

- Research respectful of, and beneficial to, vulnerable groups
The Parliament rightly expresses its democratic prerogatives when it shows interest in aligning wherever possible EC research investments with the enhancement of vulnerable members of society. The dynamic of technological progress capable of taking the needs of vulnerable people on-board necessarily has to cut across a variety of topics. Such an ambition would best be realised through cross-cutting measures, which the Parliament has been increasingly promoting in biotechnology programmes. Privileged areas under focus have been the ethical overview, and targeted policies for the vulnerable groups such as foetus, children, pregnant women, among others.

On the defensive side, ethical principles and practices have received increasing attention, until the European Commission decided to standardise and streamline a mechanism of ethical evaluation initially developed for biomedical research and biotechnology. Needless to say, the biotechnology programmes have come under special ethical focus given the topical nature of experiments involving, for example, non-human primates, human embryonic stem cells, human donors or patients in clinical trials. Thus biotechnology programmes became the place for most refinement since the time of BIOTECH II. It is no exaggeration to suggest that the overall level of ethical consciousness and best practice has been raised steadily over the period and throughout all participating organisations in the life sciences community.

On the more offensive side, the Parliament has actively participated in the inter-institutional debate modifying programme proposals and has maintained leading positions in particular when the representation of SMEs, or of women in science has been at stake.

- Management and participation in crisis prevention
One example demonstrating that research is anything but a linear exercise comes from the Commission's active involvement in crises in which biotechnology has played a role, either in crisis management, or as part of the solution. During the 1990s and the first decade of this millennium, several health crises have seriously affected Europe, and continue to do so. Some of these crises have threatened Europe in a dramatic way, such as the foot and mouth disease epidemic of 2001. Particularly traumatic for public opinion has been the regrettably famous BSE (bovine spongiform encephalopathy) debacle, commonly known as 'mad cow disease' and the TSE (transmissible spongiform encephalopathy), more generally referred to as prion diseases. Other crises have had a more global nature such as SARS (severe acute respiratory syndrome), which is a viral respiratory disease in humans caused by a coronavirus, or avian influenza informally known as avian flu or bird flu, whose major threat was that a mutation of the H5N1 virus might make it transmissible to humans and thus trigger a pandemic.

In all of these cases, the Commission rapidly engaged with other international organisations active in the area, in particular the WHO and national health authorities, to address these crises in an as coordinated and effective way as possible. The Council and the

European Parliament strongly encouraged and supported the Commission in implementing initiatives to manage, control and fight these crises. Their engagement was translated into extraordinary short times for discussing and approving the Commission proposals. Thus, several calls for research proposals on each of these diseases were launched in record times, never repeated since. Bruno Hansen, at that time Director of Life Sciences and Technologies at the Commission, showed his true leadership during these difficult periods bringing together outstanding scientific officers, such as the late Isabel Mínguez Tudela, making sure that the Commission, with the full backing of the other major EU institutions, prepared, developed and implemented research initiatives aimed at mitigating and fighting the effect of these epidemic diseases.

Towards more policy-driven biotechnology programmes

Starting from 1984, the organisation of all EC research programmes within a comprehensive Framework Programme (FP), followed by the incorporation of the latter in the European Single Act (1987), provided a breakpoint for best practice in both the design and management of research programmes. From this moment, the policy drive would be expected to come systematically from decision-makers authorised at a high level and, hence, with greater representative capacity. In theory at least, biotechnology research, and other research alike, was no longer a vanguard activity, but fell specifically into the hands of top EU leaders. This did not mean, at least until BIOTECH II, that individuals would not remain influential in their own way, providing successive biotechnology programmes an original flavour for some time at least. The pioneers, including de Nettancourt, Goffeau and van Hoeck and their expert networks still triggered specific initiatives, until the time of the BRIDGE programme, but were gradually confronted with political forces and institutional guidelines defining completely new deals. Definitely, the trend in leadership turnover meant that the Commissioners in charge went into new directions far beyond the modest ambitions of the pioneers. As the distribution of political influences effectively kept changing during the whole period, bottom-up and top-down approaches have been going up and down to variable extents, thus reflecting sometimes conflicting ideological views. The Council also took a more prominent role deliberately, as from 2000, opening a new era of Framework Programmes, including their life sciences part, in which the most legitimate players (Member States, established institutions, industry) became far more present behind the scenes of EU inter-institutional decision-making process.

Commissioners in their policy role

Before the advent of the European Research Area (ERA) in 2000, and its underlying philosophy, the series of Framework Programmes which had been hosting biotechnology programmes already appeared to be convenient instruments for planning, managing and overseeing EC research funding. They found themselves, however, surrounded by policy orientations not entirely deprived from ambiguities. The Treaty's wording (competitiveness of European industry and support to Community policies) was rather vague and was open to different interpretations, particularly when translated into operational instruments [29]. Commis-

sioners in charge have logically been using this vagueness to support directions which, in their opinion and against the background of their own experience, seemed to respond to widespread sensitivities within their own remit. At the expense of oversimplifying, one might postulate that two main attitudes animated the research Commissioners during their mandates of generally five years. While some were seen as active supporters of an industrial policy, others, perhaps more conservative but willing to understand the functioning of the research fabric in Europe, paid more attention to the modernisation of the educational, legal, international context within which front-line research was expected to blossom.

Let us take first the putative supporters of an industrial policy. One might certainly nominate in this category Commissioners Davignon (1981–85), Pandolfi (1989–92) and Cresson (1995–99). Davignon had been himself the inventor of the Framework Programme instrument, and the convener of the Industrial Research & Development Advisory Committee (IRDAC) which released the first known external opinion on the EC funding of biotechnology (strikingly in favour of upstream collaboration and basic research). But it is rather at the proximate end of this ideological lineage that visible illustrations of influence can be discerned. An illustration will be picked up for its effects on EC biotechnology research.

Commissioner Cresson in the late nineties had been the promoter of an initiative at the interface of academia and industry. This initiative gained the name of ‘Research-Industry Task Forces’. These Task Forces were trying to apply, on a macro-economic scale, a concept analogous to that contained in EC biotechnology programmes of the pioneering times. In other words, instead of just mirroring a single EC multi-partner project in an industrial context, the ambition of Research-Industry Task Forces was to mirror an entire research field, selected on the basis of promising technology breakthroughs, within a constellation of dedicated European industries. As the name suggests, task forces were not confined to a single section of the Framework Programme, but readily encompassed connected themes or areas, and went as far as identifying new priorities and examining regulatory implications. The best example here would be the creation of the task force on Vaccines and Viral Diseases which was largely fed by a sector under BIOTECH II addressing trans-disease vaccinology. The idea was not just to bring EC biotechnology research closer to industry, but to give industry a platform from which industrial strategies could somehow reorient EC funded research towards competitive advances. Strikingly, this idea has been taken up, though refined, almost twenty years later, in the Biotechnology Key Enabling Technology part of the Horizon 2020 proposal, with the aim to “Develop innovative and competitive platform technologies that would trigger leadership and competitive advantage on a number of economic sectors”. See below under Horizon 2020.

Now, let us go back to another group of Commissioners, those adhering more closely to the idea of a consistent enhancement of the whole research fabric, such as shared by the EU, Member States, autonomous institutions and industry at large. This strikingly different ideological lineage would eventually create the new vision of a European Research Area (ERA), taken over and put into practice by the EU Council after 2000 [29]. The ERA’s fathers have been mainly Commissioners Ruberti (1993–94) and Busquin (1999–2004). Their vision will prove extremely profitable to

biotechnology, in so far as integrating a wide spectrum of structural factors, though external to research in the narrow sense, which are crucial for developing a conducive environment and for ensuring societal take-up and benefit. Among these factors we find the access to complex infrastructures for research, the training and mobility of the research personnel, an opening of EC research to the world, the protection of biotechnology inventions, and a sound scientific support to regulatory measures.

Commissioner Busquin should be singled out as, in April 2000, he set-up a ‘European Group on Life Sciences’ (EGLS) [30] reporting directly to him. This group met the European Commission’s need for top quality advice on current and future life sciences and associated technologies. The EGLS was at the origin of the organisation of four European discussion platforms to explore (i) genetics and the future of Europe, (ii) stem cells and therapies for the future, (iii) sustainable agricultures for developing countries, and (iv) modern biology *versus* visions of humanity, mainly cultural determinants [31]. It further engaged in workshops on the patenting of genes, communication with the media and a periodic round-table on GMO safety research. The thinking was evident: going for well informed, educational and inclusive approaches, thus fertilising European ground for pertinent research results.

It did not escape any observer that the two distinct ideological lineages referred to above have been crossing over each other during the almost 20 year period ending in 2000. Commissioners, inspired in one way or another, appeared in an intercalated way thus inviting the following reflection. The pioneering times (BEP-BAP-BRIDGE) were those of intellectual and managerial creativity on a small scale, encouraged by Member States who took deliberate advantage of using the EC open playground as a kind of neutral test bench for cutting edge managerial experiences in research. The later restoration of a stronger policy drive (starting with BIOTECH 1) paired with greater accountability under the mandates of dedicated Commissioners, made a paradoxical evolution possible: continuity as a leading priority, but discontinuity in design and approaches. As far as life sciences are concerned, the continuous and welcome growth of biotechnology budgets, for a period at least, was overlaid by variable underpinning visions. While the old days had seen a management which tested their concepts at project level under the scrutiny of committees, the maturation period more recently was one of concept validation at entire programme level under the scrutiny of national governments through the leadership of Commissioners in charge. Typically, the European Framework programmes between FP2 and FP6 were periodically affected in both substance and procedures, depending on whether the political forces at that particular moment welcomed an objective-driven design or an instrument-driven design. The ever returning question preceding the renewal of entire programmes seems to have been that of the desired hierarchy of values: Will strategic objectives define implementation means, or *vice versa*? The former implies at programme level sufficient pooling of shared scientific intelligence on the side of EU decision-makers, the latter definitely not to the same extent. The issue of political consensus-building remained at the deep core of this high level challenge.

A typical illustration is the variable interpretation given to one criterion for project selection, that of industrial participation. The promoters of an industrial policy let the feeling spread around that

industry should effectively participate in cash or kind in all eligible proposals with the consequence that any upstream priority-setting had to be narrowed down considerably. Conversely, those coming with broader societal views tended to understand the same criterion as a requirement to secure links with industry in whatever way, not excluding that industry could step in later as a use of the research. These different interpretations were simply part of the policy development and policy evolution around an emerging area such as biotechnology.

The new drive from Council and the European Parliament

The year 2000 coincided with the launch of the Lisbon strategy, aiming at turning the European knowledge-based economy possibly into '*the most competitive one in the world*'. This turning point materialised in EC biotechnology policy in multiple ways, particularly through reversing the hierarchy of objectives (objective-driven approach) and designing sophisticated financial engineering models at programme level (instrument-driven approach).

At that time, biotechnology was no longer an objective in its own merit, and thus disappeared from the headings of EC programmes, as the decision had been made under the Fifth Framework Programme to fund biotechnology research as means rather than as a goal *per se*. From then on, biotechnology pervaded different key actions, or different themes as subsequent Framework Programmes labelled them. This strategic shift was well in line with the pursuit of a knowledge-based economy. Biotechnology fertilises different knowledge areas, whose renewed knowledge in turn drives innovation. It is worth stressing that biotechnology immersed within food, agriculture, environment or health-specific objectives did not lose support. As a matter of fact it was accumulating more financial support across themes than ever it did under a single isolated programme.

As a consequence of this approach, one can ask why in health, agriculture and food, the environment, among others, there had still been in relative terms so many successful networks and/or projects borne by prominent centres of biotechnological expertise, certainly ahead of many respected academic fields. The timeliness of biotechnology provides part of the answer, but the acquired familiarity of previous biotechnology programme users with the dynamics of EC project design and partner integration in transnational consortia must have been key to their reiterated leading positions through this new up-scaling process. Programmes of the first generation must have acted somehow as springboards for those willing to revisit knowledge areas.

Another turn is that favouring the design of complex multi-partner financial engineering models at programme level. The idea that entire programmes could, on a case-by-case basis, benefit from various forms of decentralisation, externalisation, managerial or financial partnerships, had been on the discussion table of the European Commission for a while. Biotechnology was not escaping the organisational transition of this type, using since Framework 5 national funding in conjunction with EC funding to support EU research. This was made possible through the ERA-NET scheme, based on variable configurations of Member States' programmes coming to agreement, with the view to addressing specific topics or national programmes in a coordinated way. Here again, the representation of biotechnology research resulted being exceptionally high by comparison with other fields. An outline of

ERA-NETs in biotechnology and related areas is available from Aguilar *et al.* [32]. Even more radically, one is now looking for forms of public-public partnerships, or public-private partnerships, whose first examples have come into existence under FP7 and have much to owe to the convergence of advanced technologies, biotechnology heavily included in several among the known prototypes.

The heritage of the series of the first five EC biotechnology programmes, from BEP, which started even prior to equivalent national programmes, through to BIOTECH II over a 20-year period, has made a significant impact, particularly, on the organisation of national competent authorities, institutions and other actors in research funding. In the meanwhile however, the EC Framework Programmes in general, and the biotechnology programmes in particular, are moving away from their technology-based architecture to a vision driven more by societal demands, leadership and competitiveness, and primarily organised around trans-disciplinary tasks. They are moving towards the so-called 'Bioeconomy'.

Biotechnology programmes becoming mature

Building on the foundations of excellence, independent peer-review, transnationality and industrial participation

Looking back, it is clear that the first two European biotechnology programmes (BEP and BAP) created solid foundations for the EU research and innovation activities of today. Supported projects tended to be transnational, by convenience or necessity, even though transnationality did not become an eligibility criterion in its own right until 1985. The joining of forces by participants from different Member States and internal coordination are the most innovative and important factors differentiating research supported by the EU from that supported by other agencies or by the Member States. By rendering this condition compulsory, subsequent programmes made possible not only the mere working together but also to the planning among potential participants of their scientific future together. Transnational scientific and technological cooperation is widely considered by scientific and industrial communities and by European and international funding bodies to make a very positive contribution to maximising the socio-economic impact of research [33]. To this end, the early biotechnology programmes developed a networking approach, called European Laboratories Without Walls (ELWWS), which linked together individual researchers from different laboratories and different countries to carry out multidisciplinary precompetitive research projects. The ELWW approach emphasised a free and rapid flow of information and material between participants, and incorporated joint planning and evaluation of experiments. [34,35].

The evaluation of biotechnology research proposals obviously assessed transnationality along with the other well-known selection criteria; in this connection the ever returning question concerns the competence of the evaluation system and its legitimacy to work on behalf of European tax-payers. Experience built up over three decades, regular oversight by national delegations and statutory high level programme evaluation together ensured that any biotechnology proposal was indeed evaluated in the interest of the European citizen. Based since the beginning on transnational peer-review, the evaluation system guaranteed full independence of

influence and trans-disciplinary competence, and maintained a continual struggle to achieve higher levels of transparency, quality and credibility, matching and even surpassing the standards of prestigious funding agencies worldwide [36].

While *a priori* proposal evaluation is a *sine qua non*, programme funders and managers would give as much credit to a more indirect, *a posteriori* evaluation by which we mean the extent to which the innovative developments of a project attract involvement of industry. This would not happen if the funded projects were not of sufficient quality, significance and vision. Industry was from the very beginning encouraged to become interested and to participate in research projects, either as sponsors or as full partners in the consortia. Thus, direct industrial participation increased from 6% in the Biotech I programme (1992–1994) to 17% in Biotech II (1994–1998).

Soon it was perceived that many biotechnology research results were of a generic nature whose potential applications could interest not just the individual industrial project partners but the industry as a whole. This led to the step-wise creation of the Biotechnology Industrial Platforms, as from the late 1980s. The Industry Platform concept, created and tested under BAP as a counterpart to the European Laboratories Without Walls, should not be confused with the much larger European Technology Platforms for industry, which gained popularity throughout the Framework Programme only from the late 1990s. The Biotechnology Industrial Platforms were open groupings of technology-based industries established around significant multi-partner biotechnology projects which reinforced contacts and interactions between industry and academia and which encouraged further participation by industry in the programme. The first industry platform came into existence in 1987, largely as a result of the personal energy of three leaders of industrial research, Gunary (Nickerson, UK), Veldhuyzen van Zanten (Zaadunie, NL) and Le Buanec (Limagrain, FR). The interest of these industrial representatives in the Platforms is encapsulated in their own statement at the Louvain-la-Neuve BAP conference: *“Our experience normally goes through exclusive bilateral links, each with a single university laboratory. We fail to develop links with complex and yet intellectually productive consortia as exemplified through such ELWWs”*. As many as 13 different Industry Platforms were created in the different areas and sectors of biotechnology [37].

Research becomes an EU Community policy

The features of the early biotechnology programmes described above are now perceived as normal and taken for granted, but in those times European research was fragmented in a panoply of activities supported by the different Member States, Regions, local authorities, foundations, among others. Most of these initiatives lacked coordination with each other and quite often lacked any specific targets or deliverables beyond publication of results in international journals. Europe, at least some countries, was very strong in basic science, indeed the foundations of science in general and of biotechnology in particular can largely be credited to European research; however, contrary to the USA, Europe failed to turn these fundamental discoveries into practical applications in terms of new products or processes. The industrial revolution took place in Europe, but the promises of Biotechnology and of its spin-offs were gradually moving away from our European

horizons to the USA and some emerging economies. European leaders realised that Europe was facing a maybe unique chance to support its science base and to develop the potential represented by its translation into socio-economic benefits, and were rightly proud of the Framework Programme as an instrument to do this. The Single European Act (1987) was the first major revision of the 1957 Treaty of Rome. The Act set the European Community the objective of establishing a Single Market by the end of 1992 and laid down the basis of a true science policy for Europe by establishing the aim of strengthening the scientific and technological basis of European industry and to encouraging it to become more competitive at the international level [12]. The Act encouraged cooperation between undertakings, including small and medium-size undertakings, research centres and universities in their research and technological development activities. It also inserted into the Treaties the mandate to carry out four activities that have constituted since then the backbone of European science policy:

- (a) Implementation of research, technological development and demonstration programmes, by promoting co-operation with undertakings, research centres and universities;
- (b) Promotion of co-operation in the field of Community research, technological development and demonstration with third countries and international organisations;
- (c) Dissemination and optimisation of the results of activities in community research, technological development and demonstration; and, (d) Stimulation of the training and mobility of researches in the Community.

While the adoption of the Single European Act showed the courage of the political leaders of that time, it was also supported at ground level by a group of visionaries who felt that European research could benefit immensely from the synergistic collaboration of the most innovative European brains in academia and in industry. Enters at this point the outstanding figure of Professor Paolo Fasella, director general for research from 1981 until his retirement in 1995 and probably the first high-calibre scientist to become a director general at the European Commission. A distinguished biochemist, he had been for some time a prominent research leader at the University in Rome and, notably became included in the network of contractors supported by the EC Radiation Protection Programme. His widely recognised leadership supported his vision of fabulous prospects for European collaborations as well as the need for a global science policy and its public support to develop with the external view provided by the European Commission. He enjoyed a close relationship with the key actors in most of the different circles in which the new ideas were fermenting and circulated some of the ambitious thoughts then associated with the known EC pioneers (de Nettancourt *et al.*, see above). It was no surprise, then, that he became one of the main architects and promoters of European policies and programmes of research and technological development as he took over the highest responsibilities in the EC research directorate general. It was during these years that the idea of increased European co-operation in science and technology gained substantial ground and led to European Research Framework Programmes becoming one of the main platforms for European co-operative efforts [38]. It was a fortuitous coincidence at this time that led to the fast development of a European biotechnology programme which this article is trying to portray, namely, the stochastic

alignment of a commissioner (E. Davignon) who envisioned the policy instrument, a director general (P. Fasella) who had the determination to design and to push through the timely decisions, and those three brilliant experts (D. de Nettancourt, A. Goffeau, F. van Hoeck) with their links to the scientific community who provided the direction and detailed justification for the mobilisation of efforts. And it is to Fasella's credit that his office played the role, throughout his 14 year mandate, of an incubator in which scientific elites and his own collaborators could spend unlimited hours brain-storming and reflecting on future possibilities for European research.

Management and excellence in biotechnology

The European biotechnology programmes identified fragmentation of efforts and lack of coordination as one of the hurdles preventing effective exploitation of research results and in some cases denying worldwide leadership in a particular scientific discipline or industrial sector. The ELWW concept evolved in many cases towards larger projects, which were designed to fill the gaps in scale or in structure which were preventing optimal exploitation of the results of modern biology, agriculture or industry [39]. Most of these projects were highly successful and some allowed Europe to gain worldwide leadership. Three specific examples are outlined here: sequencing the genome of *Saccharomyces cerevisiae*, biotechnology of lactic acid bacteria, and biotechnology of extremophiles.

Strategic sequencing of the genome of *Saccharomyces cerevisiae*

Sequencing the genome of *Saccharomyces cerevisiae* started with the then paradigmatic achievement of the complete sequencing of Chromosome III of yeast, published in Nature with 146 co-authors! [40]. In the journal's own words, this result, of the BRIDGE programme, could count among the few outstanding research publications marking science history over the past 120 years. There was a double rationale to this large-scale networking of European sequencing laboratories, voiced by Goffeau, who had been mobilising the relevant institutions tirelessly. The first was to deliver the first eukaryotic chromosome sequence ever completed, and the second was to involve throughout the data accumulation period the best functional biologists who undertook functional studies of the unravelling genes. The other yeast chromosomes were later sequenced in further European efforts [41]. In the late 1980s and early 1990s further sequencing projects were initiated by European biotechnology initiatives [42], namely, the industrial microorganism *Bacillus subtilis* and the model plant *Arabidopsis*, which latter turned out to be much more than an endeavour to decipher an entire plant genome. Indeed, in this case, the EC programme was catalytic as a forum, bringing together numerous plant scientists, each attached to their own pet species until they realised that plant sciences badly missed the equivalent of an '*Escherichia coli*' model to consolidate the knowledge base and use it across the fabulous diversity of the whole plant kingdom [43].

Biotechnology of extremophiles

Extremophile research has always been a priority for the European biotechnology programmes [44–46]. It has extended our knowledge and understanding of basic questions, such as the origin of

life and adaptation to extreme conditions. Biotechnological applications of extremophiles have opened unexpected opportunities for new applications in industry, for example extremophile enzymes have a large variety of applications in the chemical, pulp and paper, textile and food industries, and extremophiles have capabilities such sulphur oxidation useful for the desulfurisation of coal, and enzymes and organic compounds useful for the pharmaceutical and detergent industries. The projects on extremophiles developed in synergy with a specific *ad hoc* Industrial Platform comprising 15 European companies, which provided forum for the exchange of views on extremophile research and created opportunities for technology transfer and exploitation of research result [47].

Lactic acid bacteria

Lactic acid bacteria (LAB) are extensively used in food and feed processes because of their technological, organoleptic and shelf-life extending properties. LAB also attracted attention in relation to possible functional properties in the intestinal tract, and to their production of natural antimicrobial substances, so called bacteriocins, which open new avenues of research on biopreservation. European biotechnology programmes extensively supported multidisciplinary research on LAB with the main aim of developing controllable and improved technological traits [48–50]. Thanks to these efforts, European research on LAB achieved world leadership and attracted industry to the new opportunities for bio-business. In particular, the Lactic Acid Bacteria Industrial Platform, created around the panoply of EU funded groups, comprised 31 members including large multinationals as well as SMEs.

Public perception and safety of biotechnology

Since public opinion has important, and sometimes crucial, influence on policy, political leaders need precise and timely instruments to assess opinion on subjects of public interest, such as biotechnology. To this end Eurobarometer was designed and its 2010 survey [51], revealed that while 53% of Europeans are optimistic about biotechnology and genetic engineering, 20% consider that these will have a negative effect; 7% considered that they will not have any effect and a significant 20% responded that they don't know. These opinions have been roughly constant since the Eurobarometer surveys started more than 20 years ago.

Although an overall majority of Europeans favours biotechnology, opinion is less favourable with respect to GMOs [52]. In 2010, by combining those who 'totally agree' with who 'tend to agree', 27% supported and 57% were not willing to support GM food; 16% did not have an opinion. Comparison between 2010 and 2005 shows no substantial change in the public perception of GM food. The world's rapidly increasing population gives farmers and scientists the formidable task of satisfying an increasing demand for crop production and for non-food bioproducts while remaining sensitive to health and environmental concerns.

For three decades the EU has been supporting research to assess, scientifically and independently, the potential risks and benefits of GMOs to humans, animals and to the environment. Results are published in international scientific journals; however European Commission has published two overviews. The first, in 2001 [54], included the results of 81 transnational projects mobilising over

400 laboratories and the second [55] presents further results of 50 projects involving more than 400 groups. Overall, since 1982, the EU has invested more than €300 million in research on GMO safety through its different Framework Programmes. The main conclusion of these efforts is that GM plants and their products are not *per se* more risky than those produced by conventional plant breeding techniques [53]. The main objectives in developing the programmes on GMO safety were to respond with scientific evidence to legitimate public concerns and to the need to provide policy-makers with sound science on which to base their decisions. While a wide range of views are held on this subject, provision of reliable scientific evidence will contribute to constructive and rational debate in our societies.

Development of a strategy for biotechnology in Europe

Twenty years after launching BEP, the first European biotechnology programme, it was only in 2002 that the European Commission launched its first strategy for biotechnology [24]. This does not mean that there was no strategy before, but earlier efforts were focused on building the foundations of European biotechnology in areas such as transnationality, industrial participation, research management, reinforcing the science base and promoting industrial exploitation of results.

The biotechnology strategy marked a turning point for European biotechnology. Considered by some to be over-ambitious, it created a catharsis in which dialogue with stakeholders, policy development and research planning and management moved from being fragmented and uncoordinated to being interdependent. The biotechnology strategy was the foundation of a new thinking in Europe that led a few years later to the knowledge-based Bio-Economy in Europe (KBBE) concept [56] and in 2012 to the Commission's communication on the bioeconomy in Europe (see below) [25].

Biotechnology and society

Ethical, legal and social issues

The European Commission, member states and experts together can legitimately be proud of the spectacular progress made in biotechnology over the past 30 years. Elsewhere in this article the role of the pioneers (notably De Nettancourt, Goffeau and Van Hoek, among others.), the support of different configurations of the programme committees, the political leadership of the Commissioners in charge, and the increasing influence of Council and the European Parliament have been outlined. However, since its applications reach into society, biotechnology is not a just a scientific endeavour; some of these applications elicit both high expectations and serious concerns in our societies. Take the examples of gene and stem cell therapies and of the bioproducts and biofuels, from the health and industrial sectors, respectively. Societal debate on these issues has moved from a purely scientific and technological discussion, in which biotechnologists are more comfortable, to a discussion of values, ethics and regulation.

While supporting research activities in biotechnology and life sciences, the biotechnology programmes and the European Commission have always encouraged and engaged in an open dialogue with society and promoted informed and rational expression of different views and sensitivities. Notably, in the mid-1990s, the Commission created the ethical, legal and social issues (ELSA) unit

to develop a common research area for the various programmes in life sciences and technologies. ELSA aimed at analysing the ethical and social issues raised by applications of biotechnology, biomedicine and health research and was the first high-profile effort on these issues which have been tackled in many different ways both in budget and in structure [57].

The diversity and the complexity of the ethical issues linked with the new scientific discoveries led the European Commission to create in 1997 the European Group on Ethics (EGE), as an independent, pluralist and multidisciplinary body to advise on ethics in science and new technologies in connection with European initiatives and or policies, particularly, but not exclusively, in Biotechnology and Life Sciences. Recent opinions delivered by EGE relating to biotechnology include subjects such as synthetic biology, modern developments in agricultural technologies, animal cloning for food supply and ethics review of stem cell research projects [58]. These opinions have assisted the Commission to prepare work programmes and have contributed to the creation of an ethical framework for the scientific community in certain highly sensitive areas.

Biotechnology applications in industry, medicine, agriculture and the environment

The first 10–15 years of European support to Biotechnology research changed in the way research is carried out in Europe by bringing down barriers to transnational scientific collaboration and creating a new climate of collaboration between academic and industrial groups. However, despite the rapid progress it was clear that much potential remained to be realised in terms of unexploited opportunities. This is why the Commission, in its Fifth Framework Programme (1998–2002), launched the so-called Key Actions with the aim of integrating innovative research and technological development with their exploitation by industry for societal objectives. To strengthen European industrial competitiveness, particular attention was paid to creating small research-based biotechnology companies and entrepreneurship.

The key action relating most closely to biotechnology was called 'Cell Factory' and had a budget of €400 million. The key action connected the whole innovation chain from advanced fundamental research through technological development to practical demonstration. To achieve its objectives the key action needed to mobilise all the necessary operators, such as scientists, industrialists, start-up incubators, consumer and patients' associations and public-interest groups [59,60].

The many technology opportunities generated during the decade 1994–2004 by European biotechnology projects have been highlighted [61,62]. However, since many results were already the subject of confidential business negotiations or in the exploitation phase the real number is probably greater. Efforts to capitalise on the scientific discoveries and technological developments and to bring them to exploitation by industry or other means have inspired subsequent European programmes.

Biotechnology for Health

The main areas of health research supported under the Cell Factory were: novel therapeutic substances (new compounds, including biological production, new targets, delivery systems and drug intermediates); new therapeutic strategies (gene therapy, stem cell

therapy, immunotherapy, tissue engineering); *in vitro* alternatives to animal testing, and development of new diagnostics. Success in these fields meant that biotechnology in the Sixth Framework Programme (2002–2006) was almost exclusively focused on human health.

Around €600 million was devoted to the area of applied genomics and biotechnology for health [63]. This priority focused on the integration of post-genomic research into the more established biomedical and biotechnological approaches through the following research areas:

- Technology platforms for the development of new diagnostics, prevention and therapeutic tools;
- Rational and accelerated development of new, safer, more effective drugs;
- New *in vitro* test to replace animal experimentation;
- Development and testing of new preventive and therapeutic tools such as somatic and cell therapies, in particular stem cell therapies;
- Innovative research in post-genomics.

Some of these areas, such as stem cell research or genetic tests raised ethical issues where the European Groups on Ethics [58] delivered specific opinions, namely, for the use of human embryonic stem cells [64,65] and on umbilical cord blood banking [66]. Based on the EGE Opinions and the inter institutional discussions of the European Commission with Parliament and Council, it was decided that research involving the use of human embryonic stem cells would be funded so long as it was limited to banked or isolated cells in culture.

The pioneering work made during Cell Factory and Applied Genomics and Biotechnology for Health programmes laid the foundations of the Innovative Medicines Initiative (IMI), which is Europe's largest public-private partnership aiming to improve the drug development process by supporting a more efficient discovery and development of better and safer medicines for patients. IMI is a joint undertaking between the European Union and the European Federation of Pharmaceutical Industries and Associations (EFPIA) [67]. The Seventh Framework Programme contributes €1 billion to the IMI research programme and this is matched mainly by in kind contributions consisting mostly of research activities and worth at least another €1 billion Euro from EFPIA member companies

Biotechnology at the core of the knowledge based bio economy (KBBE)

European biotechnology over the past 30 years has been alternating between two different visions. One takes a bottom-up approach favouring the view that European biotechnology should be led by scientists to create the science base on which industry could develop their own business strategies. The other is top-down, aiming at enhancing industrial competitiveness at international level by making research programmes attractive to industry and involving industry in the research projects. Both approaches have been successful in terms of their own objectives. On one hand European productivity in terms of scientific papers has reached figures comparable with that of the US, and on the other, successive Framework programmes have seen industry more and more involved in the endeavours of EU research. However, despite this progress, economic indicators signal that the EU is

still lagging behind the US in bringing research results to the market.

The crucial element needed to guarantee the timely and successful transformation of research result into products or processes is innovation. Innovation like creativity and artistic talent can be stimulated but not be forced. Innovation is not, primarily, a question of budget, but rather a mental attitude. European leaders quickly recognised the crucial role of innovation in modern society and have taken a number of major initiatives to create a favourable environment in which innovation could flourish. The first and the most ambitious, is the Europe 2020 Strategy [68] which is about delivering growth that is smart, sustainable and inclusive. The strategy is focused on ambitious goals in the areas of employment, innovation, education, poverty reduction and climate/energy. Some targets set out in Europe 2020 have direct consequences for biotechnology research and innovation. Thus, 3% of the EU's GDP should be invested in R&D and that there should be a 20% reduction from 1990 levels in greenhouse gas emissions; 20% of energy consumed should come from renewable sources and that there should be a 20% increase in energy efficiency. Europe 2020 has set up several flagship initiatives. One of them is the Innovation Union [69].

To accompany the Europe 2020 and Innovation Union initiatives, the Directorate General for Research at the European Commission was renamed the Directorate General for Research and Innovation, highlighting the crucial importance of innovation in bringing research results into the market. The practical integration of innovation into biotechnology research was initially developed at a conference organised by the European Commission in 2005 on the 'Knowledge based Bio-economy' [70], later known as the 'KBBE'. This triggered further policy activity notably under the German and Belgian Presidencies of the EU in 2007 [56] and in 2009 [71].

The EU institutions gave full support to the KBBE concept and pointed out the need for concrete, realistic and achievable actions which would make a difference to business and to improve citizen's life. One measure to address this was to involve national and regional governments in the process. These notions are incorporated in the European Commission's proposal for Horizon 2020 [72] where the excellent science component includes the knowledge based part of the KBBE and the industrial leadership and societal challenges component includes the bio-economy part of KBBE.

The development of the KBBE concept can be considered the synthesis of the basic science and industrial application approaches that have been alternating for the past 30 years in the policy and implementation of European biotechnology. The novelty of the KBBE approach is the break with this false dichotomy. The KBBE has brought together the knowledge base and the bioeconomy as 'mission oriented research'. The KBBE does not take *a priori* any position on the kind of research to be performed, as long as it is geared to develop the bioeconomy; it may be basic or applied, consist of pilot or demonstration activities, or be combination of these. This new approach was initiated in the Seventh Framework Programme (2007–2013) and will develop further in Horizon 2020 (2014–2020).

Under the Seventh Framework Programme, the Food, Agriculture and Fisheries and Biotechnology theme has followed the

KBBE approach. This has supported a mission oriented approach to such fields as novel sources of biomass for industry; marine and fresh water biotechnology as a source of bioactive compounds; industrial biotechnology and biorefineries for bulk and high-value speciality chemicals; environmental biotechnology addressing bioremediation and the development of eco-efficient processes. The programme has also supported emerging trends in biotechnology, such as bioinformatics, synthetic biology and nanobiotechnologies, ensuring that Europe is at the forefront of biotechnology developments. The director at that time, Christian Patermann, has been the champion for the KBBE within Europe and beyond, preparing the ground for the Bioeconomy Communication (see below) a few years later. Further details of the research areas, examples of biotechnology projects supported in the Seventh Framework Programme and specific initiatives to bring research closer to innovation are given in references 32 and 73.

Cooperation beyond Europe

Biotechnology research under the Seventh Framework Programme has been very active in bringing new partners from outside Europe and in developing new mechanisms for international scientific cooperation according to country or regions involved, and the themes and areas of research. So far collaborations with 136 third country groups notably from the USA, Russia, Canada, New Zealand, Australia, China and India, where the cooperation has evolved in certain cases from project-to-project collaboration towards programme-to-programme collaboration in areas of shared interest and mutual benefit. With the USA, new ideas have been developed through the EU-US Task Force on Biotechnology research, which in its more than twenty years of existence has provided an ideal forum to discuss emerging fields in biotechnology. For a more specific description of the international scientific cooperation in the KBBE area and in biotechnology in particular, see references [32,73–75].

Horizon 2020, the bioeconomy and biotechnology

Horizon 2020

The Seventh Framework Programme ends in 2013. To signal that business does not continue as usual, and that Europe is responding to the economic crisis, addressing people's concerns and is strengthening its global position in research, innovation and technology, the successor programme is named Horizon 2020. The Commission launched the proposal for Horizon 2020 on November 2011 [72] with the aim to be fully operational at the start of 2014. The major difference between Horizon 2020 and the Seventh Framework Programme, in addition to the name, is that Horizon 2020 brings together all EU level research and innovation funding into a single programme. It will also be able to couple research and all forms of innovation, including innovation in services and social innovation.

Biotechnology will be embedded throughout Horizon 2020. While it will touch several of the 'Societal challenges', it will be at the core of the one on 'Food security, sustainable agriculture, marine and maritime research and the Bioeconomy', notably in developing the 'Sustainable and competitive bio-based industries'.

Biotechnology will be also highly visible in the 'Industrial leadership' part of the programme, particularly in the Area

'Leadership in enabling and industrial technologies', where biotechnology is identified as one of the Key Enabling Technologies (KETs).

The Biotechnology KET will focus on three major areas:

- Boosting cutting-edge biotechnologies as future innovation drivers with the aim of laying the foundations for the European industry to stay at the front line of innovation, both in the medium and long term;
- Biotechnology-based industrial processes enabling European bio-industry to develop new products and processes meeting industrial and societal demands, including replacing established ones based on other technologies and harnessing the potential of biotechnology for detecting, monitoring, preventing and removing pollution;
- Developing innovative and competitive platform technologies that would generate leadership and competitive advantage in a wide number of economic sectors.

Biotechnology in Horizon 2020 thus brings together the top-down approach through the Societal Challenges on bioeconomy and supporting sustainable and competitive bio-based industries, and the bottom up-approach with the KET on biotechnology. To be successful, both initiatives will have to develop strong interactions with each other so that no fruitful ideas are lost in the research and innovation process.

A sustainable bioeconomy for Europe

The Commission has recently published a communication on the Bioeconomy [76] to pave the way to a more innovative, resource-efficient and competitive society that reconciles food security, sustainable use of renewable resources for industrial processes and environmental protection.

Developing the Bioeconomy and spreading its benefits throughout Europe will require actions at both EU and national level, notably: Development of a policy framework and effective governance and coordination to encourage private investment and better align EU research and innovation funding to relevant sectoral policies [76].

- Research and innovation actions to implement the European Bioeconomy, in particular, support research into industrial applications and foster industrial involvement in research and innovation projects.
- Support bio-based markets, economic growth and sustainable employment by improving access to finance for research and innovation and propose incentives for industries trying to take innovative bio-based products to the market.
- Develop engagement with society and foster social innovation in the Bioeconomy, for instance, by promoting communication and dissemination of information on the advantages and risks of the Bioeconomy and by disseminating information on bio-based products.

The communication on a sustainable Bioeconomy for Europe provides a blueprint to maximise policy coherence in the EU and to bring research and innovation into the mainstream of the socio-economic development. Its successful development, including the extent to which it meets societal expectations will depend on the European Commission and Member States, but also on regional authorities, industry, farmers, NGOs, consumer associations, among others.

Conclusions

Thirty years of European biotechnology research policy, of running research programmes, and of using the results in science-based policy-making invites drawing certain conclusions. One certainly is the impact of EU research programmes on the scientific excellence of European biotechnology. Here the response must without hesitation be very positive. The originality of EU research and the features differentiating it from the research funded by the Member States is that the EU has supported activities of a complexity or scale that no single Member State could support alone. Biotechnology is intrinsically a transversal activity demanding a multidisciplinary and a multi sectorial approach. The different instruments and initiatives developed over the years with the aim of maximising the impact of the EU research efforts have changed irreversibly the European landscape of science policy and management. This would not have been possible without the regular interactions with the Member States' delegates in the programme committees, who have provided advice and guidance but who, in turn, have probably received a positive influence from continuing evaluations and deliberations with fellow members of the neighbouring countries, under the strategic approach and working practices of the European Commission services.

Paraphrasing Ortega y Gasset, a Spanish philosopher of the early 20th Century: "*Yo soy yo y mis circunstancias*" (*I am myself and my circumstances*), it could legitimately be said: "*Biotechnology is biotechnology and its circumstances*". Few scientific and technological fields have such a potential for application in industry, medicine or other societal activities. It is, therefore, not surprising that biotechnology had been so closely scrutinised by stakeholders, such as NGOs, ethicists and policy makers. The fortunes of EU biotechnology has fluctuated between periods favouring industry involvement in research and periods when the drive was to create a science base on which industry could develop its own technology and products. These two policy lines have converged in the Seventh Framework programme with the introduction of a mission-oriented approach for research and demonstration projects. This synthesis will be even more fully deployed in Horizon 2020 with the implementation of the Bioeconomy strategy with its coherent policy framework, to support the translation of research and innovation into industrial applications, and, just as significantly, a better engagement of the Bioeconomy into society.

Driven in the past 30 years by vibrant science that has revolutionised our understanding of the living world, it is difficult to imagine whether our three pioneers of EU Biotechnology (De Nettancourt, Goffeau and Van Hoek) could have foreseen such an evolution in European supported Biotechnology. Biotechnology that has nurtured such a wide spectrum of unexpected applications. Alternating political and ideological agendas have achieved rich applications revealing the public good dimension of the new 'know how'. Biotechnology is no longer an activity confined to the laboratory and is definitely showing its maturity over the past 30 years; it has become embedded in almost any activity of our modern society and the solutions and questions it raises through being disruptive of the traditional practices and of implicit paradigms of our collective thinking will require not just a scientific or technological response but a genuine social reflection and dialogue.

This short history of a European endeavour recalls the numerous enabling factors, as well as caveats, along the road of public intervention. But the late Dreux de Nettancourt, to whom this review article is dedicated, demonstrates through his unforgettable personal contribution, that European competition and collaboration moves with an engine, which cannot be fuelled with just the right dose of excellence, competence or other resource. Rather, the engine is fuelled by common human values reflecting the European utopia. Dreux impressed his fellow co-workers and interlocutors through his attention to different views and an exceptional listening capacity. He practised better than anyone else the basics of international solidarity, namely the readiness to offer his best as a lucid facilitator without having to expect anything in return. Yes, Dreux was the emblematic figure of the 'juste détournement' (diversion), denying any legitimacy to a 'juste retour' (recovery) principle.

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