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PRELIMINARY CONCEPT PAPER ON THE STATUS OF ADVANCED BIOTECHNOLOGIES IN ITALY

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State of the art

Advanced biotechnologies in the development of new therapeutics

A very simple way to measure the impact of advanced biotechnologies on the development of new drugs is to analyse the trend of regulatory authority approvals. The figure below compares the numbers of biopharmaceuticals (biologics license applications - BLAs) and traditional drugs (new molecular entities - NMEs) approved by the FDA from 1993 to 2020. It is interesting to note that in the period 1993-2000, approvals of BLAs were just 10% of those for NMEs. This figure jumped to 26% for 2001-2010, and to 30.5% for 2011-2020. Looking at just the last 5 years, FDA approvals of BLAs were more than 36% of those for NMEs.

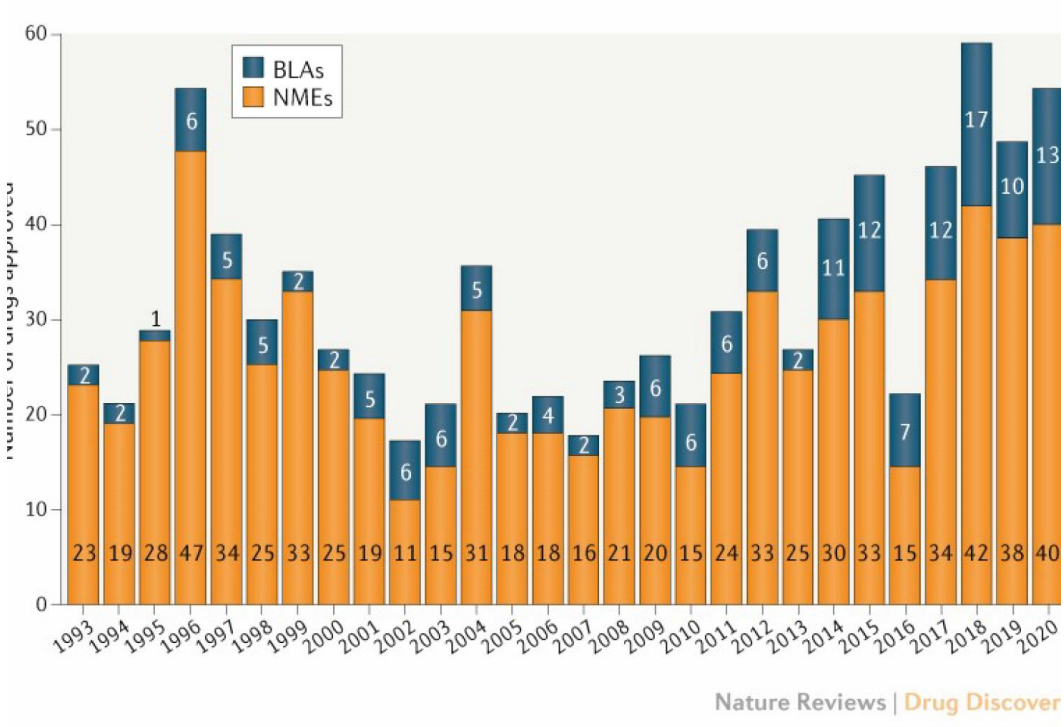
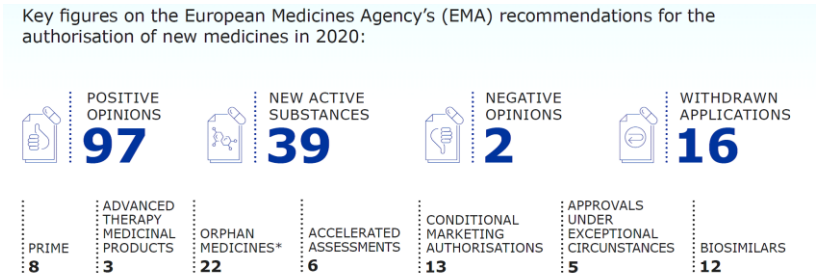


Fig. 1 | **Novel FDA approvals since 1993.** Annual numbers of new molecular entities (NMEs) and biologics license applications (BLAs) approved by the FDA's Center for Drug Evaluation and Research (CDER). See Table 1 for new approvals in 2020. Approvals by the Center for Biologics Evaluation and Research (CBER), for products such as vaccines and gene therapies, are not included in this drug count (see Table 2). Source: FDA.

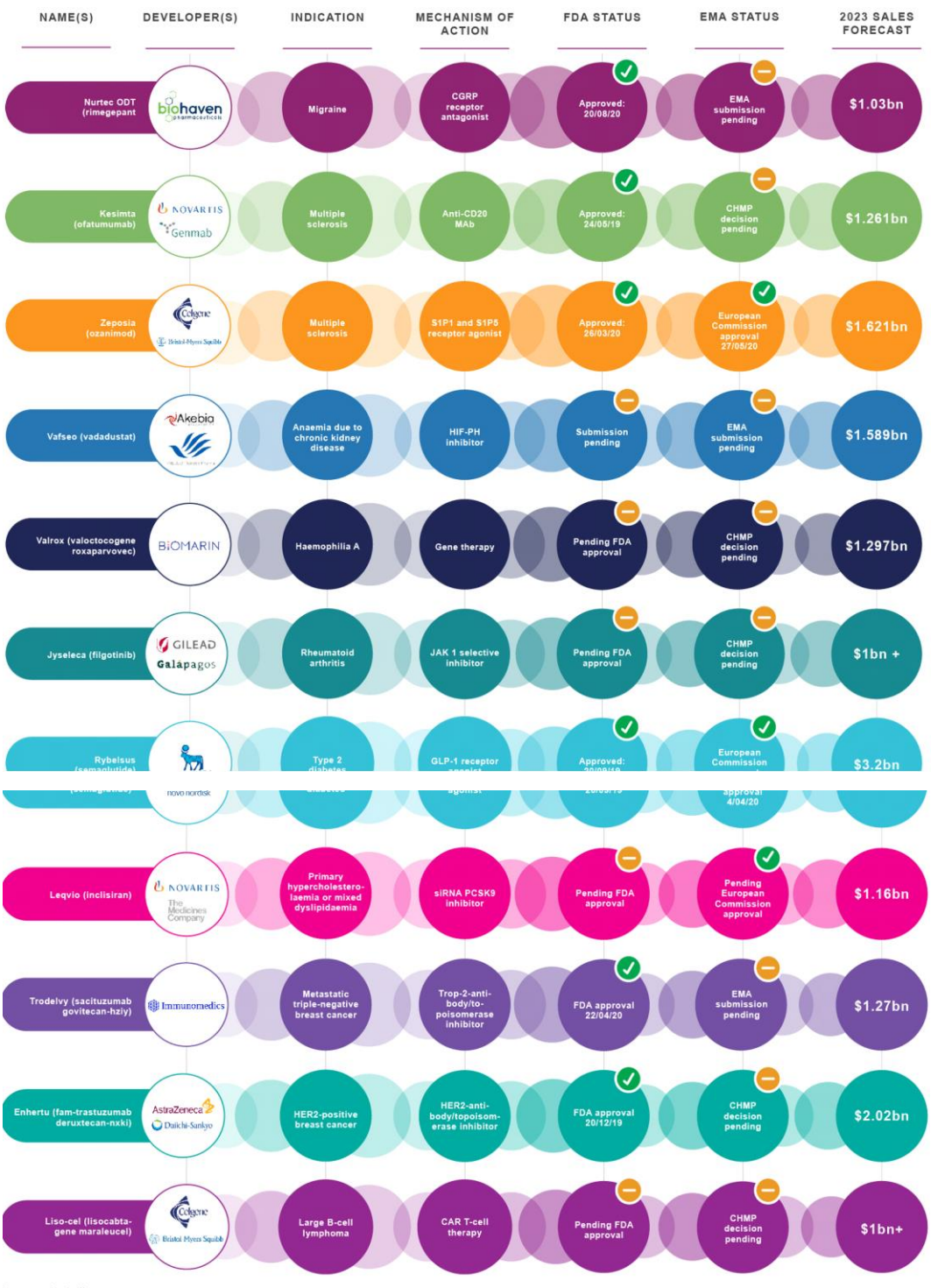
The situation in **Europe** is similar. The data reported below show the increasingly important role of biologics in the sector of orphan drugs and in advanced therapies (with three approvals in the last year), confirming the pharmaceutical industry's shift towards specialty drugs. Thirty-nine new active substances were approved in 2020.



Of these, eleven were identified as potential blockbusters (i.e. drugs that make at least $1 billion/year), as shown in the figure below:

11 potential blockbuster launches to watch in 2021

Current FDA / EMA status and 2023 sales forecast



Source: Cortellis

It is worth noting that around **half of these 11 new products are biologics**. Furthermore, there were 17,737 active projects in the drug development pipeline in 2020 (Informa's Annual Pharmaprojects Pharma R&D Review), an increase of 9.6% over 2019, which itself saw a 6% increase over the previous year.

Therapeutic monoclonal antibodies

Therapeutic monoclonal antibodies (mAbs) (https://www.uptodate.com/contents/overview-of-therapeutic-monoclonal-antibodies/print) are, to all effects, the most famous and numerous biologics. Since 1985, over 120 mAbs have been approved as medicinal products, and the list grows ever longer. The most famous mAb is Abbvie's Humira, with a turnover of €19.94 billion in 2018 alone. A number of technologies are now available for the selection of mAbs that recognise the target antigen and the production of the selected antibody for clinical use. Molecular engineering could be useful to introduce further modifications, including the generation of antibody fragments, the humanisation of antibodies produced in animals, the formation of bifunctional antibodies or the conjugation of a mAb to a drug or toxin. From the perspective of the available technologies, many of the current antibodies are recombinant drugs generated from phage libraries and are generically defined as synthetic antibodies. The same technology can also be used to generate recombinant proteins that recognise specific targets (https://ccbr.utoronto.ca/toronto-recombinant-antibody-centre).

The mechanism of action of a mAb may be based on the modulation of an immune response, the induction of cell death or the neutralisation of an infectious organism. These results are normally obtained by blocking a physiological interaction between a ligand and a receptor, or by inducing the recruitment of immune cells that can kill the target cells. In other cases, mAbs act by sequestering a cytokine, a drug or a plasma protein, preventing them from interacting with their ligand.

mAbs have a vast range of clinical indications, including the treatment of various blood disorders, solid tumours, immune disorders, hypercholesterolaemia, asthma, osteoporosis, intestinal inflammation and infections (including SARS-CoV-2).

Advanced biotechnologies: The Italian situation

The BioInItaly 2020 report produced by ENEA and Assobiotech summarises the situation as follows:

- The snapshot of biotech firms in Italy confirms the record already seen in previous surveys: there are 344 companies working in the health biotechnologies sector, representing about half (49%) of all Italian biotech companies.
- The health sector generates the most turnover [more than € 9 billion (75% of the total)] and accounts for most of the overall investment in R&D (91%) and employs more than 75% of all biotech researchers in Italy.
- There are 208 companies dedicated to biotech R&D (i.e. committing 75% or more of their internal research budget to biotech activities), of which 92% are Italian-owned: this shows how biotech has created important opportunities in early-stage research within the pharmaceutical production chain.
- There are 375 ongoing research projects involving new therapeutics in Italian-owned biotech companies. Of these, around 131 are in the discovery phase, 171 in the preclinical

development phase and 73 in the clinical development phase (14% in Phase 1, 11% in Phase 2 and 5% in Phase 3).

Italian biotech invests heavily in diseases for which there is currently no adequate therapeutic solution and is strongly oriented towards the development of therapeutic solutions for oncology. In 2019 there was also a significant development of R&D products in the field of infectious diseases.

Diagnostic products are another noteworthy sector, with 199 of all Italian biotech companies developing diagnostic products and services for human health. Of the total investments in biotech R&D in Italy, 92% is in the field of human health.

Unfortunately, 80% of the Italian biotech industry is comprised of small and microenterprises, while two-thirds of its turnover is generated by foreign-owned companies; the latter represent just 11% of the businesses surveyed and are active above all in the area of human health. Despite a total investment of €7.2 billion and an investment of around €160 million in biotech alone, the country's venture capital market still shows a gap between Italy and the main European countries.

Clinical trials in Italy

Clinical trials in Italy have remained essentially stable over the last decade (Fig. 1), although there has been a slight reduction in Phase 4 trials in the last 5 years (Fig. 2). Trials in Italy account for 19-23% of all European clinical trials, with little variation over the years taken in consideration. Around 80% of these trials are multicentre studies. Most studies conducted in Italy in 2019 [268 studies (39.9%), +0.8% on 2018] were in the field of oncology or haematology/oncology. These were followed by trials in the area of nervous disorders [57 trials (8.5%)], 11 fewer (-1.7%) than the previous year, and immune diseases [46 studies (6.8%)]. As in previous years, in 2019 more than half of the authorised trials [385 of 672 (57.3%)] involved a chemical active substance, **256 (38.1%) a biological/biotech active substance, 24 (3.6%) an advanced therapy medicinal product (ATMP) and 7 (1.0%) a chemical and biological/biotech active substance.** The study distribution trend by type of investigational drug was therefore essentially unchanged from the year before, although there was a **slight increase in the percentage of** chemical and **biological/biotech active substances** (+0.8% and **+1.2%** respectively). Of the 3,234 trials authorised between 2015 and 2019, 2,413 (**74.6%) were supported by a for-profit sponsor** (+1%) and the remaining 821 (25.4 %) by a not-for-profit sponsor. In 2019 the trend of an increasing percentage of not-for-profit trials came to a halt, **dropping 4.1% from 182 trials (27.3%) authorised in 2018 to 156 (23.2%) in 2019**.

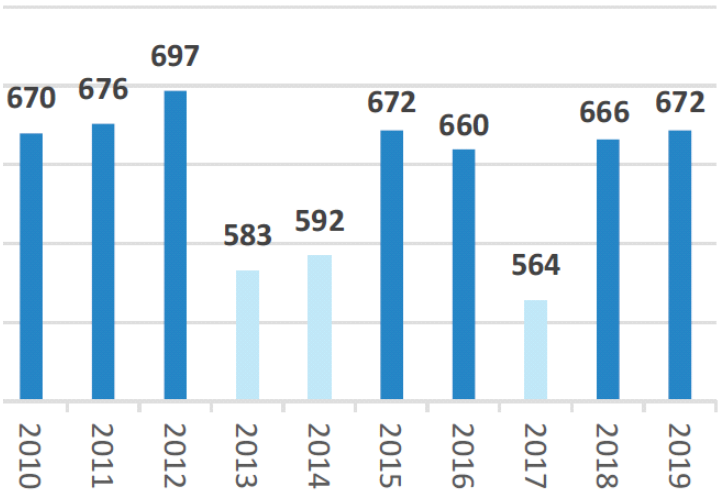


Fig. 3 Number of clinical trials authorised by the competent authority in Italy in the last 10 years (https://www.aifa.gov.it/documents/20142/1284191/19-Rapporto-OsSC_2020.pdf/ed29d6ae-8efa-7c84-088c-0eddd1853ee5)

Trials by year and phase
Clinical trials (CT) authorised in 2015-2019: 3,324

Year	Phase 1*		Phase 2		Phase 3		Phase 4		Bioeq/Bioav**		Total
	CT	%	CT	%	CT	%	CT	%	CT	%	CT
2015	69	*10.3*	224	*33.3*	306	*45.5*	68	*10.1*	5	*0.7*	**672**
2016	74	*11.5*	241	*36.5*	280	*42.4*	63	*9.5*	2	*0.3*	**660**
2017	79	*14.0*	192	*34.0*	246	*43.6*	45	*8.0*	2	*0.4*	**564**
2018	89	*13.4*	237	*35.6*	284	*42.6*	53	*8.0*	3	*0.5*	**666**
2019	74	*11.0*	248	*36.9*	307	*45.7*	43	*6.4*	0	*0.0*	**672**
Total	**385**	***11.9***	**1,142**	***35.3***	**1,423**	***44.0***	**272**	***8.4***	**12**	***0.4***	**3,234**

*In this and in all tables below, Phase 1 also includes Phase 1-2 and Phase 1-3 and Phase 2 also includes Phase 2-3.
** Bioeq/Bioav: bioequivalence/bioavailability studies.

Fig. 4 Trials authorised in 2015-2019 by year and phase

The increasing trend of **trials in rare diseases** continued in 2019, rising from 25.5% in 2017 to 31.5% in 2018 and **32.1% of the total in 2019**. **Of these, 8.3% investigated ATMPs.**

A disease is defined as "rare" when its prevalence, meaning the number of cases present in a given population, does not exceed an established threshold. In the European Union the threshold is set at 0.05% of the population, or 5 cases in every 10,000 people. The number of known and diagnosed rare diseases oscillates between 7,000 and 8,000, but this number is destined to rise alongside advances in science and, above all, progress in genetic research.

Advanced Therapy Medicinal Products (ATMPs)

ATMPs are a highly innovative drug category, due both to their configuration (genetically modified or unmodified genes and cells) and to their activity (transfer or editing of genetic information that treats the disease at its roots; cell manipulation enabling the capture of biological processes, such as immune defences and tissue regeneration, for therapeutic purposes). They typically produce significant long-lasting therapeutic effects for the treatment of serious or fatal diseases for which there are no effective therapeutic alternatives. They were originally developed above all for rare and orphan diseases, and were then extended to the treatment of cancers, such as in the case of chimeric antigen receptor (CAR)-T cells.

The properties of ATMP give rise to numerous challenges and opportunities, as summarised below; these can be seized by promoting the selection and growth of national centres of excellence for the research and clinical development of advanced therapies, as also discussed in the concluding proposals.

- **Complexity of formulation.** Some ATMPs consist of viruses modified to enable gene transfer and, in the case of cell therapies, of cells isolated from the patient and cultured and genetically modified through processes that take from a few days to two weeks. In the second case, the drug is the result of a personalised (in relation to the starting material) production process that also includes the site from which the cells were collected and the subsequent administration of the modified cells (which may be in the same or a different site).
- **Monitoring and timely management of complications.** The development of serious complications requiring lengthy hospitalisation and attentive intensive care is common with some ATMPs (CAR-T), and often linked to their therapeutic benefit. The pharma companies require clinical centres to guarantee the adequate management of such complications before permitting them to administer the ATMP. Such guarantees may mean that a clinical centre must always keep some ICU beds available for the prompt treatment of complications and/or require that the treated patient, even if in a good condition, remains at the hospital facility in order to intercept any complication as soon as possible.
- This has led to the **co-participation of the clinical facility in the drug's production and administration** in a way never seen with conventional drugs, and requires a high level of expertise. For this reason, only some specialised clinical centres for advanced therapies (***Centri Clinici Specializzati per Terapie Avanzate*** - CCTAs) are permitted to use them. It is thus important to encourage the *selection and continuous upgrade of a number of CCTAs* to ensure equal and exploitable access to the new ATMPs nationwide, avoiding inter- or intranational "health tourism" but also rebalancing the hospital network towards a hierarchy more or less equipped to manage complex therapies.
- There is also a need to promote the **advanced training of the medical and health professions involved**, creating employment opportunities for *new specialist roles: doctor-scientist* (doctors who are also researchers with in-depth training in the biology and pharmacology of advanced therapies), *pharmacist-biotechnologist* (with experience in ATMP production processes), *research nurses* and *health workers trained to use ATMPs*. The CCTAs could be catalysts for these training activities, especially if they are connected with a university or research institute. ATMP manufacturers with an interest in ensuring a centre's performance could also contribute to the training activities.
- **Innovation.** Given that many ATMPs are innovative first-in-class drugs and that they are all in the early stages of market release, under conditional registration or still in the trial phase, the CCTAs could participate in an unprecedented **pre/post-market drug development**, especially in the case of centres able to carry out advanced research. The active participation of these centres could lead not only to the identification of factors promoting or inhibiting therapeutic activity and its complications and optimisation of the ATMP's administration

(possibly in combination with other treatments), but also to the potential generation of intellectual property (IP), if the contractual conditions necessary for the participation of centres in trial design and management are created.

- From the industry's side, an **effective production and administration chain** should include centralised (national or continental) hubs for the production of starting materials (such as the vector) and a network bringing cell manipulation as close as possible to the CCTA, which itself could host a branch or franchise of the company concerned. The standardisation of the production process, its adaptation to a closed system (that can thus be carried out even in environments not classified for pharmaceutical production) and the reduction of production times and volumes are key factors in enabling the final stages of ATMP production to be progressively extended outward to a greater number of users, resulting in improved distribution and usability and a saving in costs.
- **Cell factories for ATMPs.** It is to be hoped that true cell factories for the autonomous production of ATMPs for clinical trialling will be created in at least some of the more advanced research centres and clinics. The main objective of these academic or independent cell factories should not be, as has been proposed previously, to compete with the industrial production chain by making existing ATMPs at a more contained cost. In fact, the quality and standards guaranteed by the pharmaceutical industry are probably higher than those of an academic cell factory. Furthermore, the choice between administering a registered product or an "independent" product would also be problematic from an ethical and regulatory perspective. Instead, the main aim of these cell factories would be innovation, creating opportunities for the clinical translation, at a sustainable cost, of research lines conceived in the academic environment, associated with the protection and exploitation of the IP thus generated and transfer of the technology. These selected CCTAs would have: an advanced R&D facility, a cell factory or adequate facility to carry out some or all phases of the ATMP production process, a clinical centre equipped to conduct phase 1 and 2 clinical trials of ATMPs, and skills in business development and IP protection. All these factors are necessary to enable the innovations created through research to feed effective clinical translation. An additional role of these cell factories could be the development of ATMPs for rare diseases: the high development and production costs of ATMPs tend to dampen the interest of the pharmaceutical industry in applying them to rare or orphan diseases with modest market prospects.
- **ATMP research and development hubs.** To facilitate the creation and development of ATMPs and improve access to them in Italy, there is a need to promote the growth of a belt of innovative small biotech companies around CCTAs integrated with universities and research centres. This would create a base for the application of biopharma research that makes use of the available local skills and offers employment opportunities to the new graduates trained in these centres and universities. The development of incubators for these companies should also be promoted, where public and private players can facilitate the conditions for developing research and technology transfer from the universities and research institutes. These facilitators are essential so that innovative start-ups can quickly move out of the lab to become true spin-offs able to expand their operations by managing proprietary research and development, thus generating employment. This leap requires investments orders of magnitude higher than those typical of seed capital as well as the availability of a network of contract research and contract manufacturing organisations (CROs/CMOs) to which part of the R&D activities can be contracted out. In the absence of such incubators and spin-offs, the fate of any innovations produced by translational research facilities is - in the best case scenario, in which the IP has been protected -a licence and, possibly, service agreement with an industrial partner that will control the IP, actuate its development and enjoy a large part of any economic return. The lack of any (even preliminary) proprietary clinical data at the moment of stipulating a licence will reduce its economic value and lead to a high

development risk, thus significantly reducing the research institute's immediate and future return. The launch of a joint start-up for the development and initial clinical trialling of the technology will instead offer the researchers/inventors a place on the steering committee and a greater potential economic return for the research institute and researchers in the event of any promising results that lead to the start-up's acquisition/recapitalisation. However, promotion of this dynamic requires compliance with the legal aspects that safeguard the entrepreneurial activities of researchers and lecturers in relation to universities and research institutes.

ATMPs in Italy

As of 30 December 2020, at least ten ATMPs had been approved by the EMA, of which six are marketed in Italy (Holoclar®, Strimvelis®, Alofisel®, Kimriah®, Yescarta® and Libmeldy®) (one tissue therapy, two gene therapy, three cell therapies). Refunding of their prescription charges in Italy takes from 4 months to 2 years. AIFA has awarded three (50%) of these treatments (Strimvelis®, Kimriah® and Yescarta®) the status of innovative drug. Four of the six are refunded through specific agreements (two "payment at results" and two "payment by results"). **It is worth noting that four of these ATMPs were developed in Italy, highlighting its leadership in this field: Strimvelis (autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence),** Zalmoxis (allogeneic T cells genetically modified with a retroviral vector encoding for a truncated form of the human low affinity nerve growth factor receptor (ΔLNGFR) and the herpes simplex I virus thymidine kinase (HSV-TK Mut2, **now withdrawn**))**, Holoclar (Ex vivo expanded autologous human corneal epithelial cells containing stem cells) and Libmeldy (autologous CD34+ cell enriched population that contains hematopoietic stem and progenitor cells (HSPC) transduced ex vivo using a lentiviral vector encoding the human arylsulfatase-A (ARSA) gene).**

Other innovative biotechnologies

Neurotechnology is another form of innovative technology, using biological, mechanical and information technologies to study the function of the nervous system and treat neurological diseases. Its potential applications include various biomedical contexts in areas such as the early diagnosis, prevention and treatment/rehabilitation of evolving situations caused by disease or ageing.

In this context, research into the various aspects of the nervous system - including genes, neurones and behavioural and cognitive mechanisms in both normal and pathological conditions - requires contributions from IT, robotics, neuroinformatics, cognitive science and micro- and nanotechnology. The aim is to develop analytical and experimental methods to study neurone populations and the human brain for diagnostic purposes, new devices and analytical techniques for neuropharmacology, and new assistive and rehabilitation technologies, based on advanced neural and machine interfaces and artificial systems capable of mimicking the brain's sensory, motor and cognitive functions.

The possible applications of these technologies include the development of new instruments for the diagnosis and treatment of brain injuries, devices to modulate neural activity, the design of neural prostheses, brain computer interfaces (BCIs) and bio-hybrid interaction methods, and the development of systems for the processing of biomimetic information. For example, non-invasive brain stimulation (NIBS) techniques are increasingly popular with researchers and

clinicians, with the aim of inducing changes in cerebral activity and modifying the participants' behavioural responses. NIBS techniques include transcranial magnetic stimulation (TMS) and electrical stimulation (tES), which is further categorised by the method used to administer the current, namely direct (transcranial direct current stimulation - tDCS), alternating (transcranial alternating current stimulation - tACS), or random (transcranial random noise stimulation - tRNS). NIBS is used extensively in research to investigate the functional status of cerebral systems, trace a causal relationship between the function of one or a set of cerebral areas and the performance of a task, explore the functional connectivity between different areas of the brain and induce behavioural changes by modulating neural plasticity.

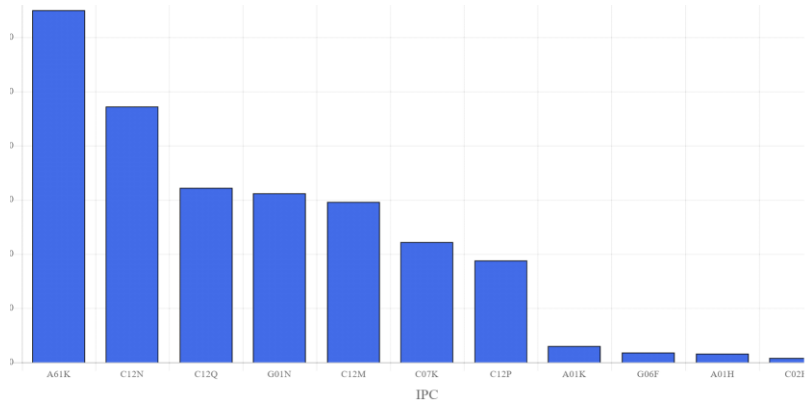
In contrast, the BCI is a direct means of communication between a brain (or, more generally, the functional parts of the central nervous system) and an external device, such as a computer. It is currently being developed and validated in clinical experiments for two different applications. The first involves Assistive Technology, which supports people with major physical disabilities in communicating with and controlling their home environment, while the second aims to develop and support cognitive and motor rehabilitation exercises. However, BCI has also been applied experimentally in non-clinical contexts including the military, with the aim of developing direct neural interfaces connecting humans and machines that enable the brain to sent complex instructions to IT systems without the need for consoles or other equipment.

In this context too, there is a need to activate platforms that are both more reactive and more equipped to deal with the issues related to neurotechnology.

OPPORTUNITIES

- The **intensity of research** in the biotech sector is considerably higher than that found for Italian industry as a whole. Investments in biotech R&D comprise 3.4% of R&D investments in the entire Italian production system, even though biotech companies only account for 0.02% of all Italian companies. There is a similarly large gap for the proportion of R&D workers against total employees: about 7 times higher for biotech companies than for the manufacturing industry as a whole. Around half (344) of the biotech companies in Italy are active in the health sector, proposing innovative medical and pharmaceutical solutions. The three macro-environments of biotechnologies in this sector are biopharmaceuticals, diagnostics and vaccines, offering out-of-the-ordinary innovative instruments for treatment, therapy and prevention.

- **The scientific output** of Italian researchers is in the top ten worldwide, highlighting their extremely high productivity (The European House - Ambrosetti, 2019).
- **There is a significant portfolio of patents filed by public research institutes working in life sciences.** Between 2009 and 2016 an average of 118 applications were filed with the Italian Patents and Trademarks Office by the biotechnology sector every year (http://www.uibm.gov.it/biotech/statistiche.html), mainly by universities and public research institutes (http://patiris.uibm.gov.it/home). In 2018 (latest available data), there were **133** applications, an increase of 7.5% on the previous year. The applications mainly pertain to healthcare and pharmaceuticals. Figure 5 provides a breakdown of the main technological sectors:



- A61K (Preparations for medical purposes)
- C12N (Microorganisms, enzymes and compositions thereof)
- C12Q (Measuring or testing processes involving enzymes, nucleic acids or microorganisms)
- G01N (Analysing materials by determining their chemical or physical properties)
- C12M (Apparatus for enzymology or microbiology)
- C07K (Peptides)
- C12P (Fermentation or enzyme-using processes to synthesise a desired chemical compound or composition or to separate optical isomers from a racemic mixture)

Fig. 5 Patent applications filed in Italy from 2008 to 2018 in the biotechnology sector, by technological sector.

CRITICAL POINTS

Snapshot of the Italian situation (with possible implications for the development of advanced technologies)

- **Low number of researchers (5.5 per 1000 employees, against an OECD average of almost 9)**
- **Much lower expenditure on R&D than other developed countries (1.4% of GDP, a percentage point lower than the OECD average)**
- **High number of small and microenterprises**
- **The companies that generate most of the biotech turnover in Italy are foreign-owned**
- **Venture capital investment in Italy is much lower than in other countries**
- **Italy's public life sciences research system is highly competitive but has only modest exploitation potential**

See the 2020 BioinItaly Report (https://assobiotec.federchimica.it/docs/default-source/biotecnologie/report-2018/2020---bioinitaly-report.pdf?sfvrsn=55644c30_8) for a more detailed analysis.

In addition to these structural aspects pertaining to Italy itself, there are a number of specific critical points:

- **Clinical centres for phase 1 trials.** On the basis of self-certification under AIFA decision no. 809/2015, there are only 81 such facilities, mainly located in the north of Italy (http://www.agenziafarmaco.gov.it/sites/default/files/2019_07_11_Elenco-Strutture-FaseI.pdf). In 2019, 74 authorisations were granted for Phase 1-2 studies. **Only 24 ATMP studies of any phase were approved, accounting for just 3.6% of all authorisations**

in 2019. Of these, 18 involved rare diseases. Most authorisations concerned the treatment of tumours (39.9%). Again in 2019, 213 (30.7%) of the 639 granted authorisations were the subject of Scientific Advice by EMA or AIFA. Unfortunately, only 8 of these (3.6% of the total for scientific advice) were Phase 1 studies. (https://www.aifa.gov.it/documents/20142/1284191/19-Rapporto-OsSC_2020.pdf/ed29d6ae-8efa-7c84-088c-0eddd1853ee5).

- **A new interface between basic research and new therapies**

  Many countries have long since implemented an integrated interface system between basic research and technology transfer (https://www.ambrosetti.eu/wp-content/uploads/TR_LiS_2018_low.pdf). In life sciences, this approach has also led to the development of new therapies, through the establishment of centres for translational science. In practice, this favours the transition of a laboratory discovery to a new diagnostic and/or therapeutic product. The first of these institutes was established in the USA in January 2005, at Penn (Institute for Translational Medicine and Therapeutics, ITMAT) (http://www.itmat.upenn.edu/about.html). It was quickly followed, in 2006, by the National Center for Advancing Translational Science (https://ncats.nih.gov/) which, through a dedicated funding programme (Clinical & Translational Science Awards Program) (https://ncats.nih.gov/ctsa), manages a network of more than 60 institutions in 31 American States.

- **Tools to break down the barriers that limit or slow the clinical development of new advanced therapies**

  - The creation of advanced facilities (including cell factories) for the production of clinical and preclinical batches of innovative drugs. Italy currently has a limited capacity to produce innovative ATMPs and drugs based on recombinant proteins, mAbs and their derivatives in the quantities necessary for clinical trials. The new facilities could be public/academic or private, but would need to be networked with the clinical centres of excellence and research centres. They would need to be approved for GMP production by AIFA and have the necessary expertise to rapidly produce medical products for clinical trials.

  - Innovative platforms for the discovery of new recombinant molecules. This concept is best illustrated by the example of a platform in Toronto for the generation of synthetic antibodies and altered proteins for use in research and therapy, starting from libraries of biological products (leads) that are then further engineered. In practice, all skills required for the screening, isolation, engineering, production and characterisation of new synthetic recombinant antibodies are found in a single centre. Such platforms could also coordinate networks of academic spin-offs and/or start-ups in the health sector.

  - Advanced facilities able to predict the toxicity and efficacy of new leads. Around 80% of new drugs fail during their clinical development, of which around 30% due to toxicity. The development of new therapies thus involves the extensive use of all available bioinformation systems, AI and traditional molecule databases in order to predict their toxicity and efficacy. These activities are then confirmed in tissue array and organoid studies that better reproduce the physiological conditions in which the new active

substance will act. In other words, this is a new kind of toxicology that could be placed at the service of the entire network of translational centres.

- Risk reduction in the development of new therapeutic products. Clinical studies are particularly lengthy and costly. For this reason, a de-risking activity is essential: from good preclinical design through to the correct collection of data for subsequent assessment by the regulatory authorities during both the trial authorisation phase and after the conclusion of the approved trials. These activities would be provided by a network of consultants with expertise in GCP and GLP. Preferential access to preclinical research establishments would also be offered as necessary.

- Effective clinical research. Clinical research requires adequate infrastructure, resources and the ability to interact with the regulatory authorities, as well as direct experience. Trial investigators must be trained, to optimise patient enrolment and accountability activities and gain familiarity with the regulatory procedures. If a trial is unable to recruit the necessary patients within the deadline, this often translates to failure. The network of Italian specialist research institutes (IRCCSs) could be a key factor in this process, but there is a need to identify and further promote those that have a facility integrated with a university or research centre and are able to ensure the effective development and exploitation of the fruits of the research.

- Collaboration and participation. The philosophy of the single researcher and single centre must be overcome. Real progress in translational activities in Italy can only be made after the activation of a dedicated network of infrastructures and partnerships through which it will be possible to collaborate with experts in all disciplines, access unique services, interact with patient organisations, meet possible investors and consult experts in the regulatory and ethical processes, who are fundamental in the development of new therapies. This will require the establishment of both research and integrated clinical development centres of excellence and a **national body** capable of coordinating the country's translational research centres while, at the same time, offering access to all the activities, including those listed above, that are necessary to achieve the objective.

PROPOSALS

- **Establishment of a National Centre for Advancing Translational Science for the biomedical area, with the following duties:**

    - Promoting the establishment of Translational Science centres/departments in universities and research centres active in life sciences.

    - Activating an annual funding programme to support these centres; this will be managed centrally and may provide grants at any time (without the need for a formal call for applications) for research activities and contracts with clinical facilities at the IRCCSs or any other public or private facilities that are authorised to conduct Phase 1-2 studies. Vouchers will also be available to cover the production costs of clinical batches, for contracts with clinical centres authorised to conduct phase 1-2 studies, and to cover the costs of CRO activities. The initial budget will be €50 million (€150 million for the first three-year period), rising annually in relation to spending power and results achieved.

- Activating investigator training programmes in collaboration with the IRCCS network and the Ministry of Health.
- Identifying and activating a network of the skills (human resources) necessary for the de-risking of clinical trials on advanced therapies.
- Facilitating meetings between University and public research institute technology transfer offices (TTOs), inventors/investigators, and Venture Capital funds in collaboration with the network of national technology clusters.
- Managing a fund for public-private co-investment in the projects with the highest probability of success, in the form of equity investments. The fund value will be up to €150 million over 5 years, with the first €30 million available in the first year and the rest in relation to the investments made. The fund may not invest in other funds, but many invest alongside other funds and/or private investors.

- **Expediting trials (especially of ATMPs), facilitating scientific advice procedures and creating the conditions and a fund to make them free of charge for small and microenterprises, not-for-profit organisations and public research institutes**
  - Discuss with AIFA the possibility of expediting low-cost Scientific Advice activities; ask the government to establish a fund to cover the costs of these activities for small and microenterprises, academic start-ups and spin-offs, public institutions and private not-for-profit organisations.
  - Survey and network all clinical facilities in the IRCCSs and other centres authorised to carry out Phase 1-2 trials of ATMPs and biologics. Identify those that are best integrated with university and research institutes and promote their further role as catalysts for clinical and translational research with advanced therapies, providing them with their own advanced facilities/cell factories.

- **Activate innovative discovery platforms**
  - The technological areas of interest pertain to **mAbs and their engineered derivatives** (mAb fragments, bispecific mAbs and conjugated mAbs) and to **all recombinant proteins with a possible therapeutic role**.
  - The second platform concerns **cell therapies**. Cell therapies are currently divided into two broad categories: stem cell and non-stem cell. Stem cell therapies generally refer to treatments deriving from haematopoietic stem cells (HSCs). The FDA has approved 8 products deriving from cord blood HSCs. There are a multitude of applications in oncology, with the pipeline of cancer-targeting cell therapies growing rapidly from 753 in 2018 to 1,011 in 2019. Cell therapies that do not derive from HSCs include Provenge® (modified dendritic cells of the immune system) and ChondroCelect® and MACI® (modified cartilage-derived chondrocytes).
  - The third platform is for **gene therapies**. The FDA has received over 900 investigational new drug (IND) applications involving gene therapy products; the availability of new viral vectors means that gene therapies are becoming an extremely important option for many patients. Many of these applications involve the use of adeno-associated viral vectors (AAVs). This crowded sector currently contains more than 50 companies and other institutions that are developing AAV-

based gene therapies. Other viral vectors for gene delivery are based on herpes simplex or retroviruses, including lentiviruses (LVs), such as in Italy.

The risks for Italy

Successful Italian businesses are now becoming attractive to international operators and are ever less accessible for the development of the national projects around which they were created. The latest examples include the acquisition by Catalent of Bristol-Myers Squibb's biologics, sterile, and oral solid dose product manufacturing and packaging facility in Agnani and the purchase of MolMed by the Japanese company AGC (both in 2020). These acquisitions should make us proud, but at the same time it is important that Italy does not become merely a "producer" of APIs and drugs but that it can also fully exploit the inventive skills of Italian researchers who, until now, have had only a limited ability to take the thorny path that starts with discovery and ends with approval of a therapy. If the conditions needed to develop this pathway are implemented, Italy could become one of the most innovative countries in Europe.