Merck – fighting disease for 350 years

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Merck, the world's oldest pharmaceutical and chemical company, is celebrating its three-hundred-and-fiftieth anniversary in 2018. Over 350 years, Merck has evolved into a leading global science and technology company in healthcare, life science and performance materials. The Merck family has remained the majority owner of the company. Merck employs approximately 50,000 people around the world and develops technologies that improve and enhance life, such as biopharmaceutical therapies to treat cancer or multiple sclerosis, cutting-edge systems for scientific research and production, and liquid crystals for smartphones and LCD televisions.

Merck grew from the 'Engel-Apotheke' ('angel pharmacy'), which was purchased by Friedrich Jacob Merck in 1668 in Darmstadt, Germany, and is still in operation today. The transformation of Merck to a research-driven industrial company was marked in 1827 when Emanuel Merck isolated and characterized alkaloids for distribution to chemists. In 1887, Merck opened its own office in New York, which gave rise to the subsidiary Merck & Co. three years later. During World War I, the subsidiary was expropriated in 1917 and has been an independent company ever since. Merck is known as Merck internationally except in the United States and Canada, where the company operates as EMD Serono in the biopharma business, as MilliporeSigma in the life science business, and as EMD Performance Materials in the materials business.

Today, Merck's Life Science division provides scientists and engineers with best-in-class laboratory materials, technologies and services, making research and biotechnology production simple, fast and safe. The Performance Materials division develops specialty chemicals for particularly demanding applications, provides groundbreaking liquid crystals as well as organic light emitting diode (OLED) materials for displays and lighting, effect pigments for coatings and colour cosmetics, and high-tech materials for the production of integrated circuits. The Healthcare division's goal is to help create, improve and prolong life, and to drive innovation in science and technology to make a lasting difference for patients and consumers. Merck develops prescription drugs and solutions to treat cancer, multiple sclerosis, infertility, growth disorders, allergies and certain cardiovascular and metabolic diseases. Merck also manufactures a series of over-the-counter products.

Merck invests more than €1.7 billion in biopharmaceutical research and development (R&D) each year. With more than 3,000 employees globally, all R&D activities within our Healthcare business are centered in four well-connected hubs in Darmstadt, Germany, Boston in the United States, Beijing and Tokyo. These centers of excellence facilitate external partnerships and represent key markets for the company and also allow us to tap into a concentration of scientific talent from local universities and life sciences companies. Together with further specialized R&D sites around the world, we create a global network that fosters collaboration, curiosity and innovation.

MERCK HAS EVOLVED INTO A LEADING GLOBAL SCIENCE AND TECHNOLOGY COMPANY IN HEALTHCARE, LIFE SCIENCE AND PERFORMANCE MATERIALS.

Patients are at the center of our efforts across the spectrum of discovery through development. Our goal is to transform innovative research into differentiated medicines that are tailored to bring value to patients in need. Guiding Merck's core research activities are the translational innovation platforms (TIPs) – oncology, immuno-oncology and immunology, which are focused on advancing new drugs through to the first application in clinical trials. Of high importance for all R&D projects is the identification of biomarkers that will lead to companion diagnostics to guide identification of patients who are most likely to benefit from a specific therapy, increasing the benefit to risk ratio.

Merck is a global oncology innovator that is shaping cancer care. The discovery efforts of our oncology TIP and our immuno-oncology (IO) TIP contribute to meeting our goal. Our immuno-oncology research focuses on discovering and developing new therapies intended to harness the immune system and activate or augment the body's natural anti-tumour responses. Efforts focus on releasing the brakes on suppressed anti-tumour responses, remodelling the tumour microenvironment to eradicate tumours, re-engaging the immune system, increasing the immunogenicity of tumours, and identifying novel drug resistance pathways including work on immune checkpoint inhibitors.

Our risk-balanced oncology pipeline comprises high-quality, selective small molecules, antibodies and antibody-drug conjugates, with strong translational research data supporting each drug's clinical development. We are developing drugs with best-in-class potential and clear differentiation in our five focused innovation clusters: oncogenic signalling, antibody-drug conjugates, DNA damage response, tumour metabolism, and tumor cell plasticity.

New approaches are being investigated by cancer researchers, including at Merck, for example by targeting the

History and future
The history of innovation at Merck

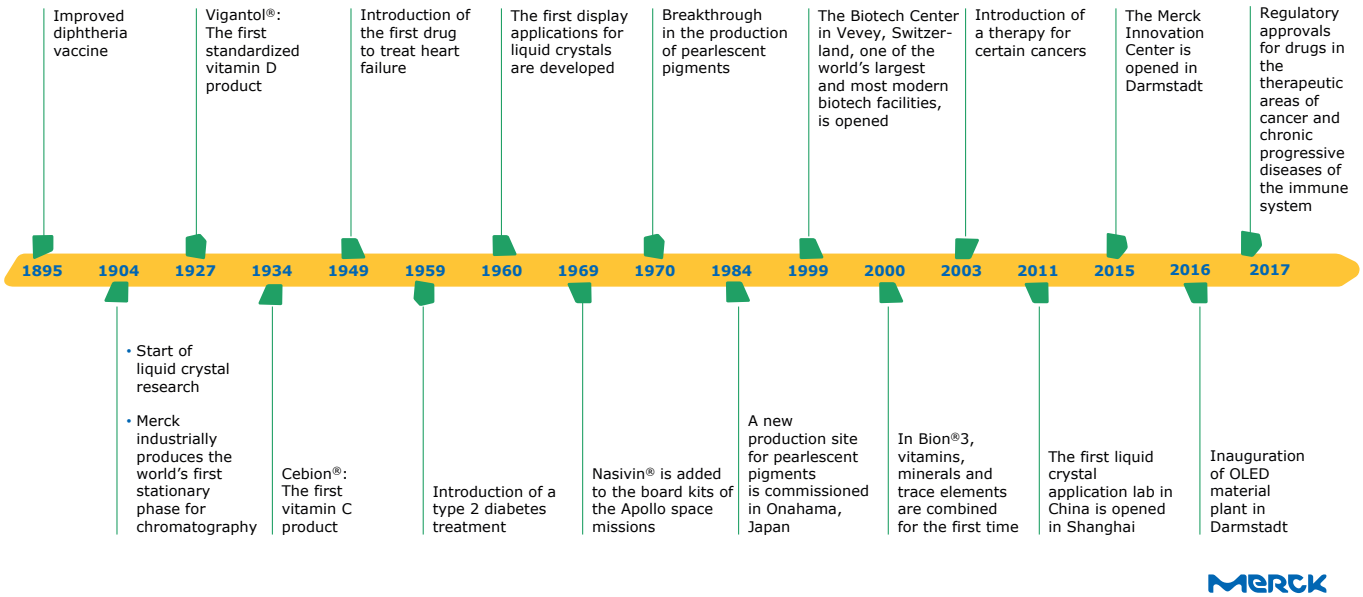

Fig. 1: A timeline showing the history of innovation at Merck.

c-Met receptor tyrosine kinase. Alterations of the c-Met signalling pathway are found in various cancer types and are thought to correlate with aggressive tumour behaviour and poor clinical prognosis. Another interesting target pursued by cancer researchers, including at Merck, is DNA-PK, a key enzyme in the double-strand break repair pathway. A DNA-PK inhibitor is designed to potentially enhance the efficacy of many commonly used DNA-damaging agents, such as radiotherapy and chemotherapies.

Merck is dedicated to delivering personalized medicine and aims to identify the patient populations who are likely to respond to treatment. Merck is also researching optimal dosing through the use of pharmacodynamic biomarkers and thereby increasing the probability of success in clinical development. Merck believes that rational combinations are the key to developing the future of new and more effective treatment options. In particular, we are focusing on the combination of our targeted therapies with chemotherapy and/or radiotherapy, other targeted therapies and/or immunotherapies.

Our IO research and early development platform – integrating research, early development and biomarker strategies – focuses on discovering and developing potential new therapies that are intended to harness the immune system and activate or augment the body's natural anti-tumour response. We are re-imagining immuno-oncology by exploring the science of immunology and oncology to investigate an array of targets with the best opportunity to improve outcomes, and make a real difference to people living with cancer. Efforts focus on checkpoint inhibitors, immune suppression from cancer cell metabolites, modulation of tumour phagocytosis, tumour myeloid cell modulation, directed co-stimulation and T-cell engagers. In the past year, R&D efforts have led to the approval of a new drug (www.fda.gov) (www.ema.europa.eu).

Our immunology research focuses on discovering drugs that modulate key pathogenic mechanisms in autoimmune pathologies and has the potential to alter treatment paradigms for chronic conditions such as multiple sclerosis, systemic lupus erythematosus, osteoarthritis and rheumatoid arthritis. We are pursuing novel pathways that modulate the immune system in a more targeted way than traditional immunosuppressants. We are developing approaches that target the innate and adaptive components of the immune system, which includes inhibiting the inappropriate immune activation that contributes to the disorder, as well as enhancing immune tolerance, which trains the body not to react to triggers. Autoimmunity researchers, including those at Merck, are pursuing inhibitors of Bruton's tyrosine kinase, which is important for the development and functioning of various immune cells including B lymphocytes and macrophages. The work is based on preclinical research and is thought to potentially be therapeutically useful in certain autoimmune diseases. For the treatment of forms of arthritis, our investigational therapies feature approaches that may facilitate cartilage repair homeostasis (a balance of regrowing cartilage

and stopping cartilage from breaking down).

In addition to the TIPs, Merck also pioneers fertility treatments, addresses unmet needs in endocrinology and is active in infectious and neglected diseases. Merck, as the world market leader in fertility treatments, continues its commitment to innovation in fertility with the ambition to help couples facing conception issues at every stage of the reproductive cycle. We are continuously improving our drug and technologies portfolio and aim to improve treatment success rates and treatment experience for patients undergoing assisted reproductive treatment.

In endocrinology, Merck pursues focused development to respond to unmet medical need in growth hormone disorders and metabolic indications. Our approach to personalized medicine is also being applied to this therapeutic area, for example by searching for biomarkers in an effort to improve the care of patients undergoing growth hormone therapy.

Billions of people currently lack access to effective and affordable healthcare. Merck has made it a top priority to improve their situation. Supporting global access to healthcare has become a strategic priority and Merck ranked fourth in the 2016 Access to Medicine Index. Through its Global Health Institute, Merck is working to address key unmet medical needs related to infectious diseases such as schistosomiasis or malaria. The treatment for schistosomiasis to date is Cesol® 600, a tablet that contains an active ingredient known as praziquantel. We produce the tablets at our plant in Mexico and also cover the transport and logistical costs involved in getting the tablets to Africa. The World Heath Organization manages, monitors and documents the distribution of treatment at the local level. In addition, Merck is developing a paediatric formulation of praziquantel, as well as new active ingredients for the treatment of schistosomiasis and malaria in addition to diagnostics for these diseases.

All the above R&D activities are rooted in our deep belief that open innovation and collaboration are instrumental in solving the world's toughest problems. Open innovation is a central part of Merck's strategy and the company has a longstanding history of working together successfully with corporate and academic partners to complement our pipeline, strengthen our technology base and enhance our scientific capabilities.

By collaborating with Mersana and Sutro, we have gained access to technology platforms for developing next-generation antibody-drug conjugates. In DNA repair, we combined our pipeline with assets licensed from Vertex in 2017 and continue to invest in both new target identification and translational research. We have an ongoing research partnership with the Weizmann Institute of Science since almost 40 years. Our research agreement with Pfizer Inc. and the Broad Institute of Harvard and MIT aims to identify biomarkers relevant to future therapies to treat lupus. Merck has recently become a member of the Structural Genomics Consortium, which supports our efforts to identify new innovative drug targets. We are working with the University of Texas MD Anderson Cancer Center to more quickly advance the development of investigational cancer therapies. With F-Star, a biopharmaceutical company headquartered in Cambridge, United Kingdom, we have recently entered into a new strategic collaboration to develop and commercialize bispecific immuno-oncology antibodies. Together with Intrexon, a biotechnology firm headquartered in Germantown in the United States, we are developing a next generation chimeric antigen receptor (CAR) T cell platform. With software firm Palantir Technologies based in California, United States, and in alliance with data-sharing platform Project Data Sphere we are leveraging the power of big data analysis, just to mention a few examples.

WE STRONGLY BELIEVE IN THE POWER OF CURIOSITY, INNOVATION AND TALENT.

Along with our commitment to open innovation we strongly believe in the power of curiosity, innovation and talent. The Merck Biopharma Innovation Cup is an annual camp at which young talent from innovation hotspots all over the world can engage with experienced Merck professionals in a meeting of the generations to brainstorm and develop ground-breaking therapeutic concepts, platforms and technological solutions covering unmet medical need. It is a valuable experience for graduate and post-graduate students to learn about R&D in the pharmaceutical industry (http://innovationcup.merckgroup.com; http://innovationcup.emdgroup.com). The programme has won several innovation awards, including the German Industry Innovation award in 2015. Merck is also hosting hackathons and start-up accelerators (https://www.merckgroup.com/en/research/innovation-center.html). Recently a special campaign has been rolled out to underline the overall importance of curiosity for progress and development

THE DEFINITION OF DISEASES IS SHIFTING AND IS INCREASINGLY DETERMINED USING MOLECULAR MARKERS.

(http://curiosity.merckgroup.com). A strong emphasis is given to the motto 'As one for patients', which is also the headline of an internal cultural change initiative.

To mark its three-hundred-and-fiftieth anniversary, Merck is sponsoring this *Nature Outlook* on the future of medicine. From early beginnings with plant extracts or the first synthetic drugs originating from the dye industry, an impressive progress in drug discovery has been achieved[1]. The twentieth edition of the World Health Organization Model Lists of Essential Medicines includes 433 drugs that are considered essential for public health needs, indicating that people across the world are benefiting from drugs that treat many different diseases. Nevertheless, tremendous medical need still remains and the speed of progress in areas of science and technology such as information and communication technology over the centuries seems to have been more prominent[2]. In past decades the productivity and sustainability of drug discovery has become a challenge. Although the number of drug development failures due to poor pharmacokinetic profiles has diminished significantly, failures due to efficacy and safety issues persist and overall attrition rates remain high[3]. Likewise, the costs for a new chemical entity are continuously rising[4].

A series of potential breakthrough technologies and trends constitute possible game changers because they have the potential to drastically affect healthcare in general and drug discovery in particular. A few examples are further elucidated below:

NEW THERAPEUTIC ENTITIES

Innovations are certainly still happening within small molecules (natural compounds and synthetic compounds) and protein drugs (monoclonal antibodies or cytokines), such as advanced library and screening technologies (for example DNA-encoded libraries and ultra-high-throughput screening), new antibody designs (for example bi/tri-specific antibodies), new antibody-like scaffolds (for example anticalin or DARPin) or the combination of both classes (antibody–drug conjugates). However, a series of therapeutic entities are emerging that have the potential to complement the armamentarium of small molecule and protein drugs. The CRISPR–Cas technology for tailored gene editing is opening the door towards genetic modification of disease genes, probiotic bacteria are harnessing the effects of the microbiome on health and disease, stem cell therapies are coming into reach and genetically modified immune cells are being applied for cancer treatment (for example CAR T cells). Finally, electroceuticals are proposed to target individual nerve fibres or specific brain circuits to treat an array of conditions.

INCREASED PATIENT STRATIFICATION

Personalized medicine is a therapeutic approach involving the use of biomarkers derived from an individual's genetic and phenotypic information to tailor drug therapy. As a consequence, the definition of diseases is shifting and is increasingly determined using molecular markers. The development is transforming pharmaceutical therapy from a one-size-fits-all approach to a tailored endeavour. Patients are stratified into increasingly smaller subsets, improving therapeutic outcome and minimizing undesired side effects – a model that is best described as precision medicine. Of all oncology drugs in development, 73% are personalized medicines[5], and 137 FDA-approved drugs have pharmacogenomic information in their labelling[6]. Technologies used for stratification are becoming increasingly sophisticated. For example, liquid biopsies can be used to help detect tumours from blood samples, and non-invasive approaches can detect disease from metabolites in the breath or urine. Such developments have their own challenges because increasingly fragmented patient populations mean that recruiting sufficient patient numbers for clinical trials has become more difficult. A series of cost-cutting payment schemes are being discussed so that healthcare systems will be able to cope with the higher costs associated with personalised treatment. A key challenge will be to ensure strong incentives for companies to continue investing in the discovery of innovative drugs that offer therapeutic options for patients in a personalized medicine context.

DIGITALIZATION

The rise of computers and machine learning, as visible in showcase examples such as IBM Big Blue, IBM Watson or Google Deepmind, has also reached healthcare. Hypothesis-free analysis of patient records or profiling multi-omics including for example genome, transcriptome, proteome, epigenome and microbiome datasets has the power to uncover new diagnostic and therapeutic approaches. *In silico* screening, which uses computers to screen drug candidates, and the prediction of compound properties are renewing drug discovery. In general, the chances of machine

learning and cognitive computing applied to drug discovery and healthcare are seen as one of the most important game changers by many analysts.

PREVENTIVE MEDICINE

From a clinical perspective, it is challenging to move away from treating diseases in which the symptoms are present, to an approach that relies on early intervention and preventive medicine. Pharmacological intervention should begin when certain disease biomarkers are moving out of the normal range, which is often decades before the first symptoms of disease become apparent. The early intervention approach has the potential to significantly reduce the cost of healthcare systems in the long term.

INNOVATIVE NEW DRUG PRODUCTION SYSTEMS

Personalizing treatment leads to changed manufacturing demands. Single use systems increase flexibility and reduce production lead times. Likewise, the development of agile, continuous manufacturing systems is predicted to be one of the most significant changes in the pharmaceutical industry in the next ten years. New options being discussed for the manufacturing of drugs that could be disruptive include magistral drug preparation, which is a model to circumvent many of the technological, regulatory and financial challenges that prevent provision of the right drug at the right time to the right patient[7].

NANOTECHNOLOGY

In the long term, advanced nanotechnology offers a series of potentially disruptive opportunities such as advanced drug delivery technologies and fully functional medical nanorobots performing therapeutic processes inside our bodies.

ANTI-AGING

Recent data have created hopes that the physical and mental aging process itself can be halted or even reversed[8]. The finding has the potential to be a game changer, disrupting the entire healthcare system and even society itself.

PANDEMIC THREAT

In the past, humanity has suffered tremendously from infectious agents. The plague or 'black death' that swept through Europe in the fourteenth-century as a result of infection with the bacterium *Yersinia pestis* was one of the most devastating pandemics in human history, resulting in the death of an estimated 75 to 200 million people. The advent of antibiotics is the success story par excellence for drug discovery. However, the emergence of multi-drug-resistant bacteria combined with a lack of new innovative antibiotics has culminated in a potentially dangerous situation. In addition, there is a continuous threat of a global pandemic created by emerging viral pathogens and the recent emergence of new viral pathogens such as severe acute respiratory syndrome, known as SARS, Middle East respiratory syndrome, or MERS, or new influenza strains are clear warning signs. Global health was discussed at the recent G20 gathering in Hamburg, Germany, and should trigger increased activities for pandemic preparedness.

Multiple activities to identify and evaluate such potential future game changers and to support the advancement of science and technology are sponsored by Merck on the occasion of its anniversary. For example, a comprehensive survey on future game changers has been performed in collaboration with *Nature*, AAAS/Science and Harvard Business Review Analytical Services and a meta analysis of the results will be published. A Harvard Business Review analytics report and a special edition of Angewandte Chemie will also be published in 2018. In addition, Merck is initiating a major scientific flagship conference called Curious2018–Future Insight that will take place in Darmstadt, Germany, in July 2018. Some of the best minds in science, technology and entrepreneurship will come together to discuss the future of science and technology and to realize the dreams for a better future (http://curious2018.com). The conference will be the birthplace of the Future Insight Prize, which will be awarded annually from 2019. The new prize will honour the most outstanding scientific achievements and ground-breaking innovations that are important for the future of humanity. In 2018 Merck is also conducting a special anniversary edition of the Merck Innovation Cup covering the fields of healthcare, life reimagined/synthetic biology, materials and solutions, digitalization and new ways of collaborating. Furthermore, a series of anniversary research grants will be available and scientists from all over the world are encouraged to apply with innovative research proposals (http://350researchgrants.merckgroup.com http://350researchgrants.emdgroup.com) or to participate in research competitions (http://350researchchallenges.merckgroup.com http://350researchchallenges.emdgroup.com).

As the world's oldest pharmaceutical and chemical company, Merck can look back at a successful 350-year history of curiosity and innovation. It is our privilege and honour to continue this path into the future combined with an invitation to partners all over the world to join forces and to work together with us to advance science, technology and medicine for the benefit of patients.

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