Pfizer's Precision Medicine Pipeline and Technology Portfolio

An interview with Mikael Dolsten and Morten Sorgaard

Balancing components in the Pfizer drug pipeline

Q. Do you anticipate that the Pfizer portfolio will tend to include more precision drugs vs broad-base blockbusters over time?

Mikael: Overall, we see an increased focus and scientific opportunity in precision therapies in several areas, driven by advances in patient stratifying biomarkers. At the same time, we believe there will be a continued role for broad based blockbusters that may still emerge in areas such as internal medicine, for example.

Our portfolio has evolved over time and is balanced across broad-based potential blockbusters, like our cardiovascular disease portfolio and vaccines, and precision medicines both from Pfizer's approved therapies, and from programs under investigation in our pipeline.

A few examples of Pfizer's precision medicines include IBRANCE® (palbociclib), our cell-cycle inhibitor for ER+ breast cancer; BRAFTOVI® (encorafenib) for BRAF+ mutated melanoma and colorectal cancer; and the anaplastic lymphoma kinase (ALK) inhibitors used to treat non-small cell lung cancer (NSCLC) such as LORBRENA® (lorlatinib) and XALKORI® (crizotinib).

At the same time, our pipeline is increasingly focused on precision-guided investigational projects:

- Recently, we were encouraged by the strong efficacy in the first Phase 3 results of our oral investigational SARS-CoV-2 protease inhibitor in COVID-19, which is being developed

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broadly for potential use in treating infected symptomatic patients or exposed individuals.

- In rare and genetic diseases, we are advancing our gene therapy platform with clinical programs in Hemophilia A, B, and Duchenne Muscular Dystrophy. We are focused on leading in this technology by bringing together the expertise in AAV vector design and development with partnerships, in-house knowledge of disease biology, and our manufacturing capabilities.
- While most biomarkers today represent a single gene product, we anticipate that during the next decade, we will increasingly see advances in biomarker signatures using data from large biobanks and machine learning algorithms to identify responders with the best benefit to risk outcomes.

Our pipeline, which is also balanced, includes, as of November 2, 2021, 94 potential new therapies or indications from phase 1 through registration, and over the next 18 months we have the potential to deliver up to 10 approvals, up to 15 pivotal readouts, and up to 15 key proof-of-concept readouts that could deliver an exciting next wave of innovation in medicines and vaccines.

We are committed to following the science and addressing the evolving unmet needs across our 5 core therapeutic areas – Oncology, Inflammation & Immunology, Vaccine, Rare Disease and Internal Medicine.

Q. What is Pfizer's position on other drug modalities – e.g., nucleic acid technologies either as drug discovery tools or potential therapies (vaccines and targeted silencing)?

Morten: We've learned over the years that getting into a new modality in a meaningful way often requires a significant investment and, in many cases, that usually involves collaborating, partnering, or making an acquisition. As we look at different modalities, we are driven by biology and the internal expertise that helps us advance in new technologies or modalities where we have the right capabilities.

The focus on build, buy, or partner allowed Pfizer to expand into new modalities like gene therapy. We've invested heavily in gene therapy over the last three to four years, largely focused on adeno-associated virus (AAV)-based gene therapies. We are also exploring combinations with gene editing to correct genetic disease, which is a promising area that we and others are pursuing with great interest.

Our work in mRNA is another example of an exciting modality Pfizer is focused on. Because we had an existing collaboration with BioNTech in flu, we were able to pivot to working to develop our vaccine for COVID-19 at the start of the pandemic. We believe mRNA technology has the potential to address a wide range of therapeutic areas, including cancer and genetic disease, and provides a strong opportunity for us.

And so we've expanded on modalities that augment already existing efforts, extending the scope of our Emerging Science and Innovation modalities by tapping into the external ecosystem. For example, we recently entered into a collaboration with Arvinas to develop and commercialize the first potential PROTAC, or PROteolysis TArgeting Chimera, estrogen receptor protein degrader. PROTAC protein degraders efficiently eliminate rather than inhibit disease-causing proteins, and in the future, have the potential to be the new endocrine therapy backbone either alone or in combination with CDK inhibitors, other targeted therapies, and/or therapies with novel mechanisms of action.

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Mikael Dolsten

Q. Can you comment on Pfizer's position on cell-based therapies – e.g., CAR-T cells – including using academic partnerships to access assets?

Morten: As mentioned, we are committed to following and advancing breakthrough science, and at the same time being strategic. In many cases, a significant investment is required to make the science successful;we can't always go "all in" on every single modality and choices must be made. I think our work in CAR-T is a perfect example of how we think about opportunities to participate in exciting modalities, even if it's not through in-house efforts.

Pfizer invested early on in cell and gene-based therapy, particularly CAR-T. Our ultimate conclusion was that CART-T fits better in biotech, which is why we made the decision to contribute our CAR-T development program assets to Allogene and enter into an asset contribution agreement in 2018. Pfizer owns a stake in Allogene and continues to see this novel approach as a promising option for patients.

Target identification and novel drug potential

Q. Which biotechnology tools (more specifically, genomics, proteomics, epigenomics) has Pfizer integrated into target discovery?

Morten: Data has matured significantly to the level where we can use them (biotechnology tools) in a flexible way across our R&D organization, particularly as we focus on human genetics and understanding the links to human disease. Pfizer has integrated a variety of biotechnology tools and data sets – including genomics, proteomics, epigenomics and transcriptomics – to enhance and accelerate our drug discovery efforts.

Data sources – like biomarkers and biobanks – are critical to these efforts, playing a role in everything from human genetics and omics analysis, to discovering and developing new precision medicines, enhancing our understanding of responses to medicines and vaccines and generating novel insights with stronger links to researchers and patients through the intersection with AI.

In July 2021, Pfizer, AbbVie, and Biogen collaborated with the UK Biobank[1] and the Broad Institute to create and release one of the world's largest browsable resource linking rare protein-coding genetic variants to human health and disease. The UK Biobank whole exome sequencing data has been generated as part of the UK Biobank Exome Sequencing Consortium, formed in 2018 and led by Regeneron, which, in addition to Pfizer, AbbVie, and Biogen, includes industry partners supporting a trend across the industry to collaborate on early-stage research to help build, improve and maintain large genetic cohorts, which have been crucial for our understanding of human biology and disease.

Pfizer is also a member of the FinnGen consortium and has had great use of the CentoMD database from Centogene to mine rare human phenotypes from individuals with heterozygous or homozygous loss of function. We have also had great use of cell type deconvolution technologies for dissecting blood cell and tissue transcript profiles to understand the autoimmune disease and how it is modulated.

Q. Can you cite an example of a novel binding site discovery by computational chemistry – that is a binding site that was

unexpected for a disease area (e.g., a direct binding site or an allosteric binding site or a regulatory site)?

Morten: We deploy computational approaches to identify allosteric sites and lead molecules routinely in our drug discovery programs by leveraging our internal expertise and have established a strategic collaboration with UCSF to help with these efforts. The techniques are based on molecular dynamics of protein structures of relevant disease targets employing our in-house High Performing Computing (HPC) environment.

Q. In which disease areas is Pfizer searching for targets for the next generation of drugs?

Mikael: An important factor in the strength of our pipeline is the decision to concentrate on **five** therapeutic areas where there is great unmet need and a strong biological foundation, and where our expertise and capabilities can be leveraged to improve the likelihood of success. We are also pushing the boundaries by focusing on new insights in diseases currently not well addressed or defined. We summarize these areas of focus below (not necessarily in any order):

First, in **Oncology** we focus on tumor biology, cancer immunology and cancer vaccines in both solid and liquid tumors, as well as tissue-agnostic approaches in precision cancer. Second, in **Inflammation & Immunology**, we are leveraging our experience in cytokine biology and diversifying into potential therapies that work to modulate immune responses in dermatology, gastroenterology, and medical dermatology.

In our third area of focus, **Vaccines**, we are pursuing high impact infections such as flu, Respiratory Syncytial Virus (RSV) and Group B Streptococcus (GBS), pioneering with RSV and GBS a novel maternal immunization pathway to protect vulnerable newborn babies from devastating infections, as well as a range of technologies such as polysaccharide conjugation, recombinant protein technology, and mRNA. Our work with respect to the Pfizer-BioNTech COVID-19 vaccine has not stopped; we continue to gather data from the studies of our vaccine in multiple age groups, and with respect to boosters to understand whether an annual vaccination may be needed to help protect people from COVID-19.

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Fourth, in **Rare Diseases**, we have a key focus on the molecular pathology of genetic diseases, pursuing multiple Gene Therapy programs under investigation with late-stage candidates in Hemophilia A and B, as well as Duchenne muscular dystrophy.

Lastly, in **Internal Medicine**, we focus on metabolic dysfunction and cardiovascular risk, cachexia, genetically defined approaches in nephrotic kidney diseases, as well as non-alcoholic steatohepatitis, also known as NASH.

We are also making **strategic investments into** Emerging Science Areas, such as Repeat Expansion Disorders, Senescence, and DNA Damage Response, where we see important opportunities and exciting science.

Licensing and partnership – Expanding access to drugs, targets, diagnostics, and technologies

Q. What are the key factors employed at Pfizer for scouting an opportunity, engaging external parties, and performing due diligence?

Mikael: We invest in areas where we see the greatest opportunity and where we believe we can deliver the best value. We forge partnerships that we believe will allow us to advance the best science, utilize our respective strengths and capabilities, and expand access to potential therapies and medicines that address patients' unmet medical needs. An ideal opportunity to tap into the ecosystem is one where each party will be allowed to do what it does best, and the sum is stronger than the parts working alone.

We have multiple external innovation vehicles including research collaborations, strategic collaborations, consortia, equity and seed investments, licensing, and acquisitions. We also have multiple models to work with academic investigators, including our Centers for Therapeutic Innovation, Emergence Science

Fund and Innovative Target Exploration Network. Together, these vehicles and models are designed to help us stay abreast of breaking science and technologies and keep the optionality to quickly jump in where it makes sense.

Regardless of the vehicle, our teams engage in a comprehensive due diligence process to evaluate potential opportunities, with several decision points along the way. After reviewing non-confidential information, the process continues with an initial screening stage to review confidential information, followed by the establishment of a dedicated internal team to conduct technical due diligence, and engage internal leadership, line reports and cross-functional partners for input. Only after the final diligence report is complete will organizational leadership provide functional endorsement to execute a deal. We work closely with our potential partners every step of the way to ensure this process, while rigorous, is as seamless and clear as possible.

Q. Can you comment on forging and managing the partnership with BioNTech as an example?

Mikael: Our research partnership with BioNTech dates to 2018, when it was focused solely on using BioNTech's mRNA platform for potential flu vaccines. That work was an important foundation for our COVID-19 vaccine program. Each company was familiar with the other's capabilities and scientific expertise, so when the COVID-19 pandemic started to come into view, we didn't hesitate to work together. We have similar cultures and can-do attitudes and were working very well together on the flu program, so we had a seamless transition to COVID-19.

We were able to collaborate efficiently and pooled resources from both of our organizations to deliver this vaccine at a speed like never before. Pfizer brought to the partnership our deep heritage in vaccine research and development (which, among other things, informed dosing decisions), decades of expertise in vaccine science for infectious diseases, as well as our global clinical development and supply chain capabilities, and global manufacturing scale – all areas that would have hindered the progress of a smaller company.

Q. How does Pfizer balance internal vs external resources (including academic organizations, government laboratories) in the discovery and development of assets (drugs, etc.)?

Mikael: Business development, partnering and collaboration is a strategic capability for Pfizer. A significant portion of our R&D portfolio has been either externally sourced or critically enabled through partnerships, and that has helped us stay abreast of breaking technologies and keep the door open to quickly jump in where it makes sense.

When it comes to BD, we are not just looking for clinical assets but are committed to early-stage R&D partnerships of all forms which are designed to strengthen the portfolio. We believe securing clinical stage assets is critical as much as accessing cutting-edge science, breakthrough technologies and early-stage top quality assets to support our long-term success and leadership.

We seek collaborations with academic institutions, start-ups, biotech companies, and others in which all parties bring complementary capabilities to achieve something none of us could do alone. We aim to build strong relationships and create flexible funding structures tailored to each partnership – sharing risk and opportunities fairly and equitably – with a singular focus on the best outcome: breakthroughs that change patients' lives.

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>
> Mikael Dolsten

Q. Biomarkers play a role in drug development and clinical diagnostics, but they are often complementary in roles – that is, few biomarkers lead to a clinical diagnostic assay. What do you look for when evaluating biomarker candidates for diagnostics? Or does the diagnostic assay drive the search for a biomarker?

Morten: Evaluating biomarkers is something that starts when a program is already in pre-clinical and early clinical development. And it's critical to start with the biology and a meaningful biomarker that is linked to the biology providing corollaries of target engagement, disease physiology modulation, disease endpoints, and/or safety parameters. With that information, we can think about the best assay for a diagnostic. For a companion diagnostic used for patient selection it is important that the technology is robust and that there is a sufficient instrument footprint to run the test worldwide where our medicines are available.

Typically, biochemical binding assays, immunohistochemistry, PCR and increasingly also next-generation sequencing (NGS) are used. Novel technologies including gene drive CRISPR assays and digital biomarkers for disease endpoints are on the horizon – CRISPR diagnostics being particularly relevant to pathogen detection.

Q. Target Sciences at Pfizer covers several overlapping areas but each with distinct information content. In addition, the data from these areas tend to be large and complex. What role do technologies like artificial intelligence, machine learning, or cluster analysis play (or all of these) play in extracting information for target discovery?

Morten: As a genomics division within Pfizer's Worldwide Research, Development, and Medical organization, Target Sciences is focused on generating quality target hypotheses, enhancing target validation, and building strong confidence-in-rationale for potential druggable targets. The group is also at the forefront of target discovery and validation through the Innovative Target Exploration Network, a Pfizer initiative designed to source cutting-edge target hypotheses in defined areas of science, resulting in early-stage drug discovery projects via collaboration with academic partners around the world. This external component combines with internal human genetics, computational biology, and functional genomics, as well as companion diagnostics capabilities, to potentially bring the best of emerging science and technologies into Pfizer's pipeline.

A critical piece to delivering pipeline projects is an effective target validation process comprising a wet lab target validation biology team leveraging our world class in vivo functional genomics team delivering about 100 mouse models per year with a focus on F0 founder phenotyping from a small team of ~ 5 FTEs.

Leveraging technologies such as artificial intelligence and machine learning can help us use multidimensional omics data to decode the functional underpinnings of genetic insights which is typically where we start. Human Genetics has matured and provides strong human biology guidance. This helps us unlock insights that allow us to better understand disease, prioritize targets and support our mission of bringing innovative new therapies to patients who need them. We use innovative approaches such as generative technologies and transfer learning to extract value from multiple underpowered data sets,

cell type deconvolution from RNASeq data sets, etc. Generative chemistry helps us create artificial molecules that we can then use to test our models and tap into DNA-encoded chemical libraries that bind anywhere on a protein or active site.

Q. Does Target Science include allosteric as well as the classical active binding sites? Are they identified through the genomic data sets or from molecular modeling approaches?

Morten: Target Sciences include allosteric and classic active binding sites. We are actively deploying modeling approaches to detect binding sites, assess drugability, and perform virtual screening to identify lead molecules. With recent advancements of AI algorithms (like AlphaFold) to predict protein structure from sequence, we are optimistic that we would be able to predict binding site from genomic data in a near future.

Q. Any closing words on: the role of technology at Pfizer in accelerating drug development or technologies on the horizon that may become part of Pfizer's portfolio?

Morten: At Pfizer, we believe using the best technology is critical as we develop potential medicines – from small molecules and antibodies to gene therapies and everything in between. Technology also has a significant impact on delivery and the manufacturing aspect and can really revolutionize how we manufacture some of the most targeted and innovative treatments that come forward. And underpinning everything is data – we operate in a knowledge-based industry and across all of our R&D efforts, ultimately what we're generating is a data file that will hopefully become part of a regulatory submission to support a potential treatment's approval.

As mentioned, right now we're focusing on technologies like mRNA, gene editing, AI and many others. As we look at the future and technologies on the horizon, we will continue to follow the science that allows us to discover, develop and deliver potential breakthrough treatments that improve patients' lives and health outcomes.

Q. Any closing comments on the plans for Pfizer's drug pipeline?

Mikael: Over the last decade, Pfizer embarked on a significant R&D turnaround effort focused on re-invigorating our R&D engine. We've taken a hard look at our productivity, sharpened our focus, and implemented gradual changes across multiple dimensions.

Today we are seeing the results clearly: we have an end-to-end new molecular entity (NME) clinical success rate of 21% – nearly twice the industry average for the year ending 2020. We more than tripled our Phase 2 success rate on a five-year rolling average from 2016 to 2020, achieving a 52% success rate in 2020 – significantly higher than the industry benchmark of 34%. And we are sustaining these levels in 2021.

We brought forward the first mRNA-based COVID-19 vaccine in record time and we continue to advance our investigational novel COVID-19 oral antiviral candidate. But we have a wide and exciting range of modalities that are allowing us to advance what we think could be multiple breakthrough treatments and vaccines. We have expertise in Gene Therapy; at the same time, we are working to expand mRNA technology beyond COVID-19 and into other infectious diseases as well as cancer and rare genetic diseases; we are working on bi-specific and multi-specific candidates. Pfizer's small molecule expertise is expanding into protein degraders as well.

So overall I think we are in a very exciting time at Pfizer and our toolbox of modalities and technologies is helping us advance potential breakthroughs. JcPM

References

1. On UK Biobank see also Journal of Precision Medicine | Volume 7 | Issue 3 | September 2021. The role of UK Biobank, An interview with Rory Collins

About Pfizer: Breakthroughs That Change Patients' Lives

At Pfizer, we apply science and our global resources to bring therapies to people that extend and significantly improve their lives. We strive to set the standard for quality, safety and value in the discovery, development and manufacture of health care products, including innovative medicines and vaccines. Every day, Pfizer colleagues work across developed and emerging markets to advance wellness, prevention, treatments and cures that challenge the most feared diseases of our time. Consistent with our responsibility as one of the world's premier innovative biopharmaceutical companies, we collaborate with health care providers, governments and local communities to support and expand access to reliable, affordable health care around the world. For more than 170 years, we have worked to make a difference for all who rely on us. We routinely post information that may be important to investors on our website at www.Pfizer.com. In addition, to learn more, please visit us on www.Pfizer.com and follow us on Twitter at @Pfizer and @Pfizer News, LinkedIn, YouTube and like us on Facebook at Facebook.com/Pfizer.

Mikael Dolsten, M.D., Ph.D., Chief Scientific Officer and President, Worldwide Research, Development and Medical of Pfizer Inc.

Mikael leads the Worldwide Research, Development and Medical (WRDM) organization at Pfizer, which is responsible for the development of all compounds through proof of concept, and provides pharmaceutical sciences, safety and medical support to the entire R&D pipeline and all marketed medicines and vaccines. WRDM comprises all Pfizer research units, including Oncology, Internal Medicine, Inflammation & Immunology, Vaccines and Rare Disease, as well as the Centers for Therapeutic Innovation. The Vaccines R&D team leads scientific efforts from discovery through registration of novel vaccines. Mikael also has worldwide responsibility for Pfizer's medical, safety and external R&D innovation, as well as science-based teams in pharmaceutical sciences, drug safety R&D, and large and small molecule discovery and development.

Mikael earned his Ph.D. in tumor immunology and M.D. from the University of Lund in Sweden, where he was Adjunct Professor in Tumor Immunology and was recently appointed Visiting Professor to advise on science and technology strategies. He serves on the PhRMA Research & Development Leadership Forum as well as on the PhRMA Foundation Board of Directors. He is a member of the board of Agilent Technologies, Karyopharm Therapeutics, Research! America and Vimian. Mikael is a member of the Board of Overseers for the Scripps Research Institute and a Foreign Member of The Royal Swedish Academy of Engineering Sciences. Since 2014, Mikael has co-chaired the Accelerating Medicine Partnership with National Institutes of Health (NIH) Director Francis S. Collins. Mikael advised the Obama Administration on R&D as well as then Vice President Biden's Cancer Moonshot Initiative to accelerate cancer research.

Mikael is a named inventor on several patents and has published approximately 150 articles in international journals

Morten Sorgaard

Morten Sogaard heads up Pfizer' Target Sciences group with primary focus on target and biomarker generation for Pfizer R&D, combining internal capabilities in human genetics, functional genomics, computational biology and diagnostics with external innovation e.g. through dedicated innovative target exploration networks (ITENs).

He was previously responsible for strategic technology and oncology collaborations and Pfizer WRD's overall platform technology and informatics investment strategies, and co-led several Pfizer-wide strategy initiatives on Precision Medicine and scientific technologies including gene therapy

Morten was previously at Pharmacia in Lund, Sweden. Morten moved to AstraZeneca in 1998, where he headed up the Molecular Sciences Department in Mölndal, Sweden. In 2004 Morten moved to Boehringer Ingelheim in Connecticut as VP and global head of enabling technology and a member of BI's global research leadership team. He also briefly served as Head of R&D Informatics.

Morten received his Ph.D. in Biochemistry from the University of Copenhagen in the Carlsberg Laboratory with a focus on heterologous protein expression, enzyme structure and function. He subsequently did postdoctoral studies at Sloan Kettering Institute in New York.