EPIGENETICS
AN OPPORTUNITY TO TARGET MASTER REGULATORS OF CANCER BIOLOGY

Cancer
- Leading cause of death
- Biggest economic impact on healthcare
- Chromatin biology underlies cancer pathogenesis

Interview
Dr James E. Bradner

The Belfer Collaboration
Building a complete epigenetic platform

Epigenetics & Cancer
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3 Questions to
Dr Joanna Lisztwan
In this fourth DDup issue, we delve into the exciting new field of epigenetics, where Evotec has embarked on a novel collaboration model with Dana-Farber and the Belfer Institute for Applied Cancer Science to identify the next generation of epigenetic drug targets. Evotec brings to the table a wealth of drug discovery and biomarker discovery experience, providing an industrial edge to the drug hunting process. The Belfer Institute, in alliance with the Dana-Farber Cancer Institute, contributes target validation workflows, in vivo models and genomic data to support identification of patient stratification biomarkers. One of the advantages of the model is that it allows us to rapidly progress novel targets from target validation stage all the way through to identification of a pre-clinical drug candidate.

Epigenetic drug therapy promises to provide patients with more durable therapeutic responses and even reversal of drug resistance. However, the struggle for clinicians and industry alike remains how to identify responsive patients. We feel our collaborative framework is ideally positioned to identify cancer-relevant epigenetic targets, select responsive cancer subtypes and discover candidate patient stratification biomarkers. We are especially excited about the ability to apply our state-of-the-art proteomic platform to epigenetic biomarker discovery. With a large number of unbiased target and biomarker discovery approaches, we are well-positioned to positively impact the clinical application of epigenetic drugs.

We look forward to entering into a productive dialogue with academic experts, industry partners and open innovation alliances to see this critical field progress rapidly for the benefit of cancer patients. I hope you enjoy reading this latest edition, and as always please don’t hesitate to contact us.

Yours sincerely,
Werner Lanthaler on behalf of the management team
In the past years a large number of targeted cancer therapies have been introduced into the clinic with the aim to stop proliferation and induce apoptosis of cancer cells. In combination with early diagnosis, these novel treatments have led to a clear increase in cancer survival rates. However, this has been countered by the emergence of resistance to targeted therapies and a lack of effective therapies in highly lethal cancers of the pancreas, lung, or liver which together account for the death of one third of cancer patients. Therefore, we may have reached a crossroad in cancer therapy, where administering cytotoxic and/or cytostatic drugs to a tumour cannot be the final therapeutic solution. In recent years, novel treatment paradigms targeting the immune system, cancer stem cells and epigenetic mechanisms have been introduced into the clinic, with the promise of achieving significant improvements over current approaches. In this issue, we focus our attention on epigenetic approaches, where the opportunity to eliminate cancer can be achieved through the modulation of multiple pathways at once.

Epigenetics refers to heritable changes in gene expression that are not reflected in changes to the primary DNA sequence. Epigenetic mechanisms are therefore master regulators that control the expression of multiple genes or even portions of the genome and thereby define the state or ‘phenotype’ of cells and tissues. The core unit of the epigenetic framework is chromatin, the structured assembly of DNA around histones. Factors involved in chromatin remodeling include histone writers, readers and erasers and DNA methylation modulators. In broad terms, post-translational modifications are applied by writer enzymes, removed by eraser enzymes and recognized by reader proteins leading to recruitment of protein complexes. It is the interplay of the relevant epigenetic players which define a biochemically reversible epigenetic code which is responsible for regulating cell differentiation, growth and survival. Not surprisingly, we have learnt that all cancers carry epigenetic modifications generally called the ‘cancer epigenome’. These modifications appear to be an early event in carcinogenesis, driving tumour cell survival, genetic instability and adaptability. Existing evidence even suggests chromatin modification, not DNA methylation, is the primary driver of tumour suppressor gene silencing.

The reversibility of the epigenetic code has dramatically impacted the landscape of potential therapeutic approaches for cancer. Growing pre-clinical and clinical evidence indicates that targeting epigenetic processes reflects an increased sensitivity to chemotherapy with all trans retinoic acid (‘ATRA’). This unique, retinoic acid-driven differentiation of APL cells re-activates endogenous cellular differentiation programmes leading to extensive epigenomic reprogramming. The ability to program a response in cancer cells even with short term therapies is a unique feature and advantage of epigenetic therapies that has created significant excitement in the field to further explore the possibilities of targeting epigenetic regulators in cancer.

Although DNMT and HDAC inhibitors have opened novel therapeutic opportunities, the field is still seeking to target additional oncogenic pathways and optimise patient identification strategies. Several key challenges remain in the field of cancer epigenetics: (i) unravelling the gene-specific role of chromatin associated reader, writer and eraser proteins, (ii) validating them as therapeutic targets and (iii) consequently defining a target patient population for developed drugs. Several protein families are currently of strong research interest within the industry because of their role and eraser proteins, (ii) validating them as therapeutic targets and (iii) consequently defining a target patient population for developed drugs. Several protein families are currently of strong research interest within the industry because of their role and the potential to target the long-disputed dormant cancer stem cell populations. The FDA has already approved the use of DNA methyltransferase (“DNMT”) and histone deacetylase (“HDAC”) inhibitors in myelodysplastic syndrome (“MDS”) and cutaneous T-cell lymphoma (“CTCL”), respectively. Although high doses of these drugs are toxic to patients, when applied at low therapeutic doses which induce differentiation pathways, patients not only have durable responses but also fewer adverse events, permitting extended dosing regimens. Emerging clinical evidence would also indicate epigenetic targeting agents can be combined safely at low doses. More specifically, DNMT and HDAC inhibitors can be applied sequentially with other targeted agents and chemotherapeutics to enhance responses and most interestingly begin to show significant durable responses even in advanced, heavily pre-treated solid tumour populations, suggesting a reversal of drug resistance.

The precedent for cellular differentiation therapy already exists for acute promyelocytic leukemia (“APL”) where patient 93% rate of remission and an astounding 75% cure rate when combining chemotherapy with all trans retinoic acid (“ATRA”). In this example, retinoic acid-driven differentiation of APL cells re-activates endogenous cellular differentiation programmes leading to extensive epigenomic reprogramming. The ability to program a response in cancer cells even with short term therapies is a unique feature and advantage of epigenetic therapies that has created significant excitement in the field to further explore the possibilities of targeting epigenetic regulators in cancer.

The emerging biology of histone demethylases (“KDMs”), specifically, points to strong links with cancer initiation and maintenance, promotion of a reversible drug-resistant state and maintenance of the stem cell state. Evotec and its collaborator have therefore invested in the development of a proprietary platform to further validate these promising new targets for cancer and link selective inhibitors of these enzymes with the right patient population. A component of this work is the development of industry-leading mass spectrometry methods to specifically assess classes of epigenetic enzymes and their substrates, as well as support the identification of epigenetic-relevant biomarker candidates for monitoring efficacy and patient stratification.

Recognising that we have potentially reached a crossroad in cancer therapy, Evotec has positioned itself to make significant contributions to the field of cancer epigenetics and epigenetic drug discovery. Collaborating with leading institutions in the field, Evotec aims to not only identify selective drugs for critical cancer drivers, but also make advancements in the identification of relevant epigenetic biomarkers for the appropriate positioning of drugs within the clinic. To this end, our scientists benefit from a leading technology platform, robust assay systems as well as a unique mass spectrometry platform with the ability to characterise histone marks, methylomes and acetylomes.
The Belfer Institute ("Belfer") for Applied Cancer Science at Dana-Farber Cancer Institute ("Dana-Farber"), a Harvard Medical School affiliate, was established in 2006 with a visionary commitment from the Robert A. and Renee E. Belfer Foundation. The mission of the institute is to accelerate cancer drug discovery and development by bridging the science from world-class Dana-Farber cancer researchers and premier external partners in drug discovery and development. As such, Belfer is a biotech-like organisation embedded within Dana-Farber.

The mission statement of Belfer is well-reflected in the leadership team, namely co-Scientific Directors Pasi Jänne, MD PhD and Kwok-Kin Wong, MD PhD and Director of Research Jessie English, PhD Dr Jänne and Dr Wong are both world-renowned leaders in lung cancer treatment, with seminal contributions to the field both academically and clinically. Dr Wong additionally is an internationally recognised leader in the development of mouse models of cancer. Dr English complements their expertise with her extensive experience in leading target discovery, validation and drug discovery efforts in the pharmaceutical industry. Together, they work closely with premier Dana-Farber investigators such as Dr James E. Bradner, who has already pioneered seminal research in the field of epigenetics. As a result, Belfer gains early access to breakthrough discoveries, applying rigorous validation methods to align with the large resource investment needed to initiate drug discovery efforts.

The biology of chromatin regulation is complex. However, the breadth of in vivo and in vitro technologies available at the Belfer place it in a unique position to work through the intricacies of epigenetic regulation in cancer cells to support drug discovery on novel epigenetic drug targets. Belfer has extensive expertise exploring target biology and validation through the use of RNAi technology and is applying this approach to the field of epigenetics. A key component of this research involves matching target biology to genetic context of the tumour cell, thereby delineating a potential clinical path for a specific drug candidate. To support this work, Belfer has an extensive collection of genetically annotated tumour cell lines and access to a unique collection of mouse tumour models, including patient-derived xenograft ("PDX") models and genetically engineered mouse models ("GEMMs") with driver oncogenes that overexpress or ablate various chromatin regulators. The in vivo models especially provide a platform to evaluate the biology of various chromatin modifiers in the context of specific cancer genotypes, using RNAi or drug treatment validation approaches as appropriate. Finally, Belfer’s Translational Research Laboratory ("TRL") has extensive expertise in developing blood-based genomic and proteomic biomarkers supporting patient/disease identification strategies and pharmacodynamic studies. The TRL works closely with Belfer scientists and partner drug discovery teams early in the drug discovery process to progress the development of biomarker candidates for clinical application.

The partnership between Evotec and the Belfer Institute is not only based on a novel collaboration model that completely aligns the interests of both partners, but also merges Belfer’s strengths in oncology disease biology and Evotec’s strengths in drug discovery. Evotec’s industrialised drug screening and characterisation assays, medicinal chemistry experience and proteomic platform will be particularly important in discovering candidate compounds and biomarkers for advanced biological studies.
James E. Bradner, MD, is an Assistant Professor in Medicine at Harvard Medical School as well as a Staff Physician in the Division of Hematologic Malignancies at Dana-Farber Cancer Institute. The present research focus of the Bradner laboratory concerns the discovery and optimisation of prototype drugs targeting cancer gene regulation. The clinical objective of the Bradner group is to deliver novel therapeutics for human clinical investigation in hematologic diseases.

Dr. Bradner received his AB from Harvard University, his MD from the University of Chicago and a MMS from Harvard Medical School. He completed his postgraduate training in Internal Medicine at Brigham & Women’s Hospital, followed by a fellowship in Medical Oncology and Hematology at Dana-Farber Cancer Institute. Following additional post-doctoral training in Chemistry at Harvard University and the Broad Institute with Prof. Stuart Schreiber, Dr. Bradner joined the research faculty of Dana-Farber in 2008.

Recent research has been published in Nature, Cell, Nature Chemical Biology and the Journal of the American Chemical Society. He has authored more than twenty United States patent applications, licensed to five pharmaceutical companies, and is a scientific founder of Acetylon Pharmaceuticals, SHAPE Pharmaceuticals, Tensha Therapeutics and Syros Pharmaceuticals.

Dr. Bradner’s awards and honours include the Damon Runyon-Rachleff Innovation Award, the Smith Family Award for Excellence in Biomedical Research, the Dunkin Donuts Rising Star Award and the HMS Distinguished Excellence in Teaching Award. He is a member of the American Society of Clinical Investigation, the American Society of Hematology, the American Chemical Society and the American Association of Cancer Research. His recent research has been published in Nature, Cell, Nature Chemical Biology and the Journal of the American Chemical Society. He has authored more than twenty United States patent applications, licensed to five pharmaceutical companies, and is a scientific founder of Acetylon Pharmaceuticals, SHAPE Pharmaceuticals, Tensha Therapeutics and Syros Pharmaceuticals.

Cord Dohrmann, CSO of Evotec ("CD"): The field of epigenetics, especially cancer epigenetics, has exploded in the past decade. Your lab has made critical contributions to the field during this time. What in your mind are the key discoveries which helped to establish epigenetics as central to carcinogenesis?

JB: All pathways critical to cancer cell growth and survival are encoded by coordinated transcriptional programmes in the nucleus, which are themselves embedded in the context of tissue specification. In other words, oncogenes cooperate with cell type determinant to provoke all the hallmark phenotypes of cancer. The implication of this is that the hardwiring of a tissue is a key facilitator of oncogenesis. Epigenetics, or chromatin biology, has emerged as a central and underlying theme of all cancer pathogenesis for three reasons. First, growth pathways carry out growth and survival programmes. The structure of the tissue’s epigenome cooperates with dominant oncogenes to elaborate all of the hallmark phenotypes of cancer. Second, cancer genome sequencing has identified a truly disproportionate frequency of somatic alterations affecting gene regulatory factors. I estimate that 40-45% of all altered genes in the cancer genome encode gene regulatory factors. Third, the prevalence of mutations is even more striking. One should consider that the most commonly activated or amplified oncogene in cancer is c-Myc and the most commonly altered gene in all of human cancer is p53, both of which are gene regulatory proteins. For all of these reasons it is quite clear that we must redouble our efforts to understand gene regulation and the interplay between chromatin function and oncogenesis.

CD: What benefits or advantages do you see in targeting epigenetic mechanisms in cancer over other approaches? For example, are there specific cancer types you feel will benefit most from this approach?

JB: The low hanging fruits in epigenomic drug discovery are the products of somatically altered genes: EZH2 in non-Hodgkin’s lymphoma, NSD2 in multiple myeloma and BRD4 in NUT midline carcinoma. Beyond these obvious candidates, there are a
number of targets which are showing context-specific cancer dependencies. A striking illustration is the DOT1L lysine methyltransferase, which itself is not somatically altered in cancer but has emerged through a decade of chemistry and cellular biology as an Achilles’ heel in mixed lineage leukemias. The story of DOT1L is very clear in that it implies that chromatin factors are critical collaborators to as yet undruggable gene regulatory oncogenes. As yet, we have not developed technologies to systematically identify and validate chromatin cancer dependencies but this is an exciting and emerging area of research. There are therefore three major reasons to target epigenetic factors in cancer: first, they are commonly somatically altered, rendering them obvious targets for cancer drug development. Second, they are common and critical cofactors for undruggable gene regulatory oncoproteins. And third, there’s a suggestion in the literature that undruggable gene regulatory oncoproteins are common and critical cofactors for tumor initiating cells. These elusive cells have been characterised to date by altered gene regulatory proteins, which must surely reflect a distinct chromatin architecture. We know that targeting upstream signalling proteins in cancer can generally provoke meaningful responses but very rarely allows for tumour eradication. For this and other reasons we believe that molecules that target the hardwiring of the cancer cell, such as epigenetic therapies, hold great promise alone and in combination.

CD: We have still much to learn about the reprogramming of cancer cells via epigenetic regulators. What do you see as the biggest opportunities and challenges?

JB: There is so much opportunity in epigenetic drug discovery and the chemical biology of gene regulation. Our field is just exploding with biological insights, new biochemical capabilities, creative disruptive technologies as well as first insights into how chemically to modulate the function of target proteins.

CD: Thank you for your time.

Dr Cord Dohrmann is Chief Scientific Officer and Member of the Management Board of Evotec. Dr Dohrmann has spent over 20 years in biomedical research at leading academic institutions and in the biotech industry.
Perturbations of epigenetic mechanisms, e.g. DNA hypermethylation, changes in histone modifications, mutations or abnormal expression of epigenetic regulators are frequently observed in various types of cancer. Histones, in particular, have been widely shown to contain a plethora of covalent posttranslational modifications (“PTMs”) that influence the compactness and accessibility of the chromatin, the majority of which are methylation or acetylation events. An intricate pattern of these PTMs is the basis of the so-called histone code which governs the recruitment of histones to certain promoter regions as well as the recruitment of regulatory proteins to histones. For example, trimethylation of histone 3 lysine residue 4 (“H3K4”) is associated with active gene transcription, whereas trimethylation of H3K27 results in tightly compact forms of chromatin which is typical for gene silencing. Regulatory proteins include writer enzymes (such as demethylases) and reader proteins which recognise these marks and use them as docking sites (such as bromodomain-containing proteins). Understandably, any aberrations to these mechanisms within the disease state will result in global changes to epigenetic homeostasis. As a newly evolving field, the development of drugs to reverse these changes has raised challenges around mode-of-action (“MoA”) studies, selectivity and most importantly biomarker discovery.

The past decade has seen a major advancement in mass spectrometry (“MS”)—driven protein assessments to support the characterisation, optimisation and biomarker discovery for drugs directed against epigenetic targets. The advantage of our industry-leading workflows hinges mainly on the comprehensive and quantitatively accurate data sets which are generated, satisfying stringent industry requirements. These include proteome-wide identification of acetylation and phosphorylation sites, and ongoing development of ubiquitination and methylation assessments. To date, we have successfully applied global proteome and PTM analysis to defining drug MoA and biomarker candidate identifications in combination with proprietary bioinformatic tools. Similarly, quantitative co-immunoprecipitations and target deconvolution studies are aligned to guide existing drug discovery programmes within the Company. Histone PTMs have a critical role to play in gene expression. Evotec’s proprietary HistoneScout™ platform enriches histones to gain a robust, comprehensive view on various covalent histone modifications. The MoA for a DOT1L methyltransferase inhibitor was validated with this approach, where a reduction of H3K79 methylation in leukaemic cells could be measured by MS. Moreover, HistoneScout™ provides a rich source of mechanistic information on a global histone level, including cross-regulation of other histone PTMs in the same experiment. The technology, therefore, allows one to (i) validate drug MoA, (ii) identify substrates for epigenetic enzymes, (iii) explore novel biomarkers candidates and (iv) elucidate metabolite effects on the histone code.

Our unbiased MS approach enables new clinical concepts for patient stratification within the epigenetic space. Proteome-wide identification of the target spectrum of an epigenetic drug, global analysis of PTMs and the potential to identify epigenetic biomarkers allows a holistic view on epigenetic modifications which is currently unrivalled in its depth in industry. Therefore, Evotec looks forward to contributing to a more efficient and effective progression of epigenetic drugs through pre-clinical and clinical development.

### BIOMARKER DISCOVERY MECHANISMS FOR EPIGENETIC DRUGS

- **Evotec Cellular Target Profiling** (target deconvolution)
- **Quantitative interaction and selectivity profiles**
- **Mode-of-action studies**
- **HistoneScout™ histone PTM analysis**

### Results

![Graph](image)

Treatment of MV4-11 leukaemia cells with the DOT1L-inhibitor EPZ004777 reveals global changes to proteins. Significance analysis was performed on regulation of protein expression (left), post-translational modifications on non-histone proteins (middle) and post-translational modifications on histone tails using HistoneScout™ (right). Based on the mean rank test, red symbols indicate significant regulation.
TECHNOLOGY OVERVIEW

What we can deliver

TACKLING EPIGENETIC TARGETS WITH A BROAD PLATFORM OF TECHNOLOGIES
Evotec benefits from far-reaching drug discovery and biomarker discovery experience, providing an industrial edge to the drug hunting process. The Belfer Institute, in alliance with the Dana-Farber Cancer Institute, contributes target validation workflows, in vivo models and genomic data to support identification of patient stratification biomarkers.

1. PROPRIETARY EVOLUTION™ HIT IDENTIFICATION PLATFORM
   - 24,000 fragment library
   - Sub-libraries for e.g. metal-binding
   - Orthogonal screening with NMR, SPR and RapidFire™

2. EXPERIENCED STRUCTURE-BASED DRUG DESIGN PLATFORM
   - Computational support for structure and ligand-based approaches
   - Rapid generation of crystal systems
   - Integrated medicinal chemistry teams

3. BROAD DRUG DISCOVERY PLATFORM
   - RapidFire™ label-free mass spectrometry
   - Biochemical and biophysical screening
   - Characterisation of binding dynamics
   - Epigenetic target-based cellular assays e.g. HDACs

4. SOPHISTICATED DRUG EVALUATION PLATFORM
   - Cancer, primary and stem cell systems
   - Opera® HCS customised script writing
   - Epigenetic phenotypic readouts e.g. differentiation, histone marks

5. INDUSTRY-LEADING PROTEOMICS PLATFORM
   - HistoneScout™ global histone mark profiling
   - Evotec Cellular Target Profiling® of drug MoA
   - Biomarker candidate discovery (proteomic and post-translational marks)
   - Quantitative analysis of epigenetic complexes by immunoprecipitation
   - SRM (“selected reaction monitoring”) for pre-clinical validation

LEADING EPIGENETIC DRUG DISCOVERY PLATFORM
Perfect complementation of skills and capabilities

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CANCER IS A LEADING CAUSE OF DEATH WITH A HUGE ECONOMIC IMPACT

- Approx. 12.5 million new cancer cases in 2008 worldwide
- Estimated amount of deaths of 7.6 million (about 21,000 a day)
- By 2030 the global burden is expected to grow to 21.4 million new cancer cases and 13.2 million cancer deaths.
- The total economic impact of premature death and disability from cancer worldwide was $ 895 billion in 2008.
- Direct medical costs are not included, which would further increase the total economic impact caused by cancer.

Second leading cause of death in 2008 was heart disease with 7.3 million deaths.

Heart diseases led to an economic loss of $ 753 billion in 2008, 19% lower than cancer.

THE TWO LEADING CAUSES OF DEATH IN THE US – ALL AGES (RATES ARE PER 100,000)

The historically big gap between heart disease and cancer in the US has nearly been closed over the last 30 years.

If one only considers people younger than age 85, cancer has already surpassed heart disease as the primary cause of death in the US in 1999!

COST OF CANCER CARE BY PHASE OF CARE – ALL AGES IN THE US (PER YEAR IN BILLIONS)

The US cost of cancer care is substantial and expected to increase because of population changes alone. Based on growth and aging of the US population, costs of cancer diagnosis, treatment and follow-up are projected to reach $ 158 to 207 billion in the year 2020, an increase of at least 27% over 2010 according to the NIH. If newly developed tools for cancer diagnosis, treatment and follow-up continue to be more expensive, medical expenditures for cancer could reach or even surpass $ 207 billion.

ESTIMATED AGE-STANDARDISED INCIDENCE AND MORTALITY RATES OF BOTH SEXES WORLDWIDE

According to the American Cancer Society there were an estimated number of 1.66 million new cancer cases and approximately 580,000 cancer-related deaths projected to occur in the US in 2013.

The graph highlights the worldwide incidence rate of numerous cancers having dramatically low survival rates. New therapeutic drugs are urgently needed.

E.g. the 5 year survival rate of pancreatic cancer patients is 6%, for small cell lung cancer patients 6.6%.

One in four deaths in the US is due to cancer. The lifetime probability of being diagnosed with an invasive cancer is higher for men (45%) than for women (38%).

Current epigenetic drug market situation

- The first epigenetic drug, Azacitidine, a DNMT inhibitor, was approved by the FDA in 2004
- Three more epigenetic drugs have been approved up to date: Decitabine (2006, DNMT), Vorinostat (2006, HDAC), Romidespin (2009, HDAC)
- Azacitidine and Decitabine are the most successful selling epigenetic drugs with revenues of approx. $ 1.1 billion in 2012
- Approx. 40 drugs considered to be direct epigenetic modulators are currently in clinical development (five in phase III)
- All current epigenetic drugs are primarily under evaluation in cancer indications
- Clinical efficacy in solid tumours in combination with chemotherpay is emerging, reflecting a reversal of drug resistance
INTRODUCTION

DR JOANNA LISZTZWAN

SHORT SUMMARY

OF SCIENTIFIC CAREER

Dr Joanna Lisztwan obtained her PhD in molecular biology at the Friedrich-Miescher Institute, Basel, Switzerland, focusing on cancer-related E3 ubiquitin ligases, their role in protein degradation and cellular transformation. Her research publications include papers in EMBO, Genes & Development, Nature Cell Biology and Nature.

JoiningNovartis Oncology Research in 2003, she was project leader for the p53-Mdm2 protein-protein interaction inhibitor project. Successfully integrating a multidisciplinary approach, she led the programme from screen to the identification of a clinical candidate with accompanying pre-clinical strategies for predicting patient responsiveness in the clinic.

Joanna joined Evotec in 2011 as Research Leader Oncology, where she oversees biology on existing oncology programmes at Evotec, both client-funded and internal. More recently, Joanna took over responsibility for the Belfer collaboration, centred on epigenetic targets.

I. One key disease area of Evotec is oncology, especially cancer epigenetics. What is so special about Evotec’s scientific approach?

There is no question that effective, non-toxic cancer therapies remain a pressing medical need. The majority of patients diagnosed with cancer today will receive a combination of treatment approaches, including surgical resection, radiotherapy, chemotherapy and targeted therapy. However, while cancer deaths have been on the decrease since the 1970s, patients are still faced with relapse after an indeterminate period of time. At Evotec we feel more durable responses are required, and we are therefore investing into areas of drug discovery which promise to provide these, such as cancer immunotherapy and epigenetics. In order to do this well, we are bringing several cutting-edge technologies and platforms into the table which together we believe will deliver durable therapies. Within the epigenetic space, we are specifically making use of our mass spectrometry platform for both sensitive hit identification screens as well as characterisation of drug-target interactions in a cellular context. Moreover, we aim to monitor differentiation responses and histone mark changes on a truly industrial level. Using our expertise with primary and iPSC cells, we are in a position to evaluate a drug’s mode of action on a phenotypic level in various cell types of interest, and potentially also identify novel targets and/or biomarkers. The ultimate aim is of course to translate all these in vitro discoveries against select targets into in vivo efficacy and eventually clinical efficacy.

2. How will you contribute to finding new drugs in this highly interesting field of epigenetics?

With our growing interest in epigenetics, my efforts have become increasingly centred on leading and expanding the Belfer collaboration and exploring any opportunistic targets in the epigenetics space. As a result, selecting key epigenetic targets and leading cross-disciplinary, global teams positions me in a unique way to contribute to the newly evolving field of epigenetic drug targets. However, the possibility to take on a novel drug target class is compelling but also very daunting. At Evotec, we have a long history as a drug discovery service provider for industry, spanning activities from target identification all the way through to clinical candidate selection. Going hand in hand with this expertise is a steadily expanding epigenetic platform which seeks to address the mode of action and profile of epigenetic specific drugs, as I mentioned already. Undoubtedly, Evotec is well-positioned to undertake drug discovery on existing and novel epigenetic enzyme classes. However, it is the truly unbiased manner by which we can do this which gives me added confidence, where novel chemical hypotheses can be generated from fragments, our proprietary compound collection or simply structure-based drug design. The combination of strong structural biology and computational chemistry groups as well as rapid internal decision making allows us to efficiently progress drug discovery projects.

3. What will your collaboration with the Dana-Farber/ Belfer Institute look like?

The Dana-Farber Cancer Institute is an associated Belfer Institute for Applied Cancer Science are recognised internationally for their critical contributions to basic research and translational medicine in a broad number of cancer subclasses, we aim to “industrialise” the target identification, validation and inhibition process for epigenetic drug discovery. In the process, we are confident of building up a leading team of scientists and drug discovery experts with a critical understanding of epigenetic mechanisms which can be translated into ground-breaking novel cancer reprogramming approaches.