INTRODUCTION

Cutaneous T-cell lymphomas (CTCLs) are non-Hodgkin lymphomas of mainly mature skin homing CD4+ T cells. The current WHO classification comprises eight main types of cutaneous T-cell lymphomas. The most frequent subtype is Mycosis fungoides (MF) with about 60% of all cases. Sézary syndrome (SS) is another well-known CTCL subform including 5% of all CTCL cases.

The diagnosis of CTCL is based on a combination of clinical, histopathological and molecular features and is challenging especially in early stages of the disease. As a result, the median time between initial symptoms and primary diagnosis is 3-4 years.

The disease progression is greatly diverse between patients. For about two-third of MF patients, the disease stays indolent in early stages with limited skin lesions and a normal life expectancy. Around 6% per year progress to advanced stages with tumors on the skin.
and involvement of the blood, lymph nodes and visceral organs. This progression is generally associated with poor prognosis.[4,5]

The pathogenesis of cutaneous T-cell lymphomas is not clear. Overall, the disease seems to be based on a poly aetiological process. This is supported by the following findings: antigenic stimulation in predisposed patients has been discussed and investigated for a long time[6]; however, it has not yet been sustainably confirmed. Brazzelli’s research group found indications that specific HLA alleles may predispose to the development of MF and that certain alleles may be prognostically relevant. In particular, HLA-DQB1*05 seems to be associated with a worse prognosis.[7,8] Further work has focused on molecular metabolic pathways.

2 | COMPLEX MUTATIONAL LANDSCAPE IN CTCL

In recent years, the genetic changes in CTCL were explored.[9-18] The majority of the work focused on the genetic changes in SS patients (85% of the sequenced patients), while MF patients represented only a minority in the cohort (around 11%). The reason for this stark contrast between disease incidence and representation in the sequencing cohorts might be due to technical constraints. Malignant cells in SS cases can be enriched to high purity by FACS sorting, while skin biopsies from MF cases are very heterogeneous and contain only a small fraction of malignant cells. Nevertheless, genetic changes in MF patients (at least in tumor stage patients) were successfully assessed by 30x covered whole-genome sequencing (McGirt, Torres). Additionally, protocols for enrichment of, for example CD3+ cells from biopsies exist and were already applied in MF cases (de Masson). Further application of these enrichment methods might enable the analysis of very heterogeneous MF cases thus substantially increasing the knowledge of the genetic changes in MF.

The current data situation of genetic changes in CTCL shows a great deal of heterogeneity between individual patients (Table 1).[13] Various copy number variations (CNV) and single nucleotide variations (SNV) in multiple genes involved in multiple signalling pathways were documented. Recurrently mutated signalling pathways include JAK-STAT, MAPK, T-cell receptor, TNF receptor and NFκB signalling. Further mutated cellular processes are chromatin remodelling and modification (eg DNMT3A) as well as cell cycle checkpoints (eg CDKN2A) and genomic integrity processes (eg TP53). Interesting observations from the studies were that the recurrence of individual mutation or even mutated genes was quite low. For example, the gene most commonly affected by SNVs in SS is TP53 with an incidence of “only” 12%.[13] The other interesting fact is the high abundance of CNVs (10x more abundant than SNVs, 9). These mutations are also partly more recurrent than SNVs. For example, the loss of regions on chromosome 17 containing TP53 is present in around 40% of the cohort from.[9] Supplementing the genetic changes in CTCL a plethora of changes of the transcriptome or chromatin was detected. This includes the overexpression of TOX (thymocyte selection associated HMG-box) in SS and MF, which could be used to discern these diseases from benign inflammatory diseases. On a genome scale, a clear distinction between malignant and normal CD4+ cells in terms of chromatin accessibility and patterns of transcriptions factor activation were shown.[19]

These studies were summarized by R. Stadler and R. Stranzenbach to give a precise view of the current knowledge in the understanding of the molecular pathogenesis of CTCL.[20]

These genetic changes lead to T cells that show apoptosis deficits and a consequent continuous expansion. During this process, the malignant cells show increased differentiation into T helper type 2 cells with corresponding cytokine production of interleukin 4 and 13 and resistance to normal cell control mechanisms.[21]

All these experimental and scientific efforts are intended to discover novel biomarkers and meaningful therapeutic targets to be addressed in the treatment of cutaneous T-cell lymphoma and, of course, to elucidate the complexity of the pathophysiology of CTCL.

One of the clinical approaches resulting from the genomic knowledge of SS is a diagnostic approach by Weed et al. They designed a panel of FISH probes against eleven GCNAs that had been recurrently identified in up to 79.9% of patients with Sézary syndrome. This fish assay detected GCNAs in 92% of the patients that met B2 blood involvement criteria by the International Society of Cutaneous Lymphoma (ISCL).[22]

One therapeutic approach is the inhibition of miR-155. This micro-RNA is upregulated in tumor MF compared to early stage MF and might be a trigger for MF progression into advanced stages. An oligonucleotide inhibitor of miR-155, cobomarsen, coordinate regulates multiple survival pathways to reduce cellu lar proliferation is already in a phase 1 trial in cutaneous T-cell Lymphoma.[23]

Another therapeutic approach is proposed by Nicolay et al. Here, the hypothesis is that combined inhibition of the antiapoptotic mediator B-cell lymphoma 2 (Bcl2) and the NFκB pathway can overcome cell death resistance. As the hyper-activated NFκB pathway

| TABLE 1 | Park et al identified 55 genes in lymphomagenesis including a gain of function mutation in RLTPR that potentiates T-cell receptor signalling |
| --- | --- |
| Genomic analysis of 220 CTCLs | BCOR, KDM6A, SMARCB1, TRRAP |
| Chromatin remodelling | CD 58, RFXAP |
| Immune surveillance | MAP2K1, NF1 |
| MAPK signalling | PRKCB, CSNK1A1 |
| NF-KB signalling | PI3-kinase signalling |
| PI3-kinase signalling | PIK3R1, nVAV1 |
| RHOA/cytoskeleton remodelling | ARHGEF3 |
| RNA splicing | U2AF1 |
| T-cell receptor signalling | PTPRN2, RLTPR |
| T-cell differentiation | RARA |
is a common survival factor in CTCL, this approach might be applicable for CTCL therapy. The used drug is dimethyl fumarate and inhibitor of the NFκB activation.[24,25]

Further interest was directed on T-cell receptor sequencing. This genetic feature poses a unique biomarker in T-cell lymphoma (or B-cell lymphoma in case of B-cell receptor sequencing). T-cell receptor clonality assessment is used for a long time in CTCL diagnosis [26]; in recent years, the NGS-based clonality assessment[27,28] is increasingly replacing the gel based methods. To improve the results from T-cell receptor sequencing (eg minimization of amplification bias), multiple protocols were developed. In 2019, the euroclonality group published their new gold standard for NGS-based TCR clonality analyses, including spike-in DNA and controls to deal with bias and polyclonal background.[29,30]

In addition to using T-cell receptor "only" for diagnostic purposes, the data might also be used as a prognostic marker. Adele de Masson et al measured the tumor clone frequency in lesional skin by high-throughput sequencing of the TCRB gene and identified the clone frequency as an independent prognostic factor in early stage patients of cutaneous T-cell lymphoma.[31]

### 3 | HOW HAS THE FIELD PURSUED THIS LINE OF RESEARCH IN THE MEANTIME?

Based on these results, there is a critically unmet need to identify putative molecular targets. The genetics for this special lymphoproliferative disease with these different manifestations remain obscure. Therefore, the development of a powerful targeted therapy is very difficult.

In the period between 2018 and today, additional studies towards the genetic changes in CTCL were carried out. This includes the analysis of additional seven Sézary syndrome cases by whole-exome sequencing. Over all their cases, they found 551 non-synonymous SNVs split across 525 genes. Several of these mutated genes are part of the pathways already known to be affected in CTCL like JAK-STAT and PI3K/AKT signalling. Additional mutations were found in peroxisome proliferator-activated receptors and fibroblast growth factor receptors adding up to the great complexity and heterogeneity of SS (Table 2B).[32]

In Mycosis fungoides, nine cases were investigated by whole-genome sequencing.[33] Here, the most notable result was the recurrent deletion of HNRNPK and SOCS1, and both inhibitor of the JAK-STAT signalling pathway were detected. This result showed especially for MF the great importance of dysregulated JAK-STAT signalling on the MF pathogenesis. (Table 2A).[33]

Furthermore, the genetic landscape of gamma delta T-cell lymphoma was investigated by performing whole-genome, RNA and T-cell receptor sequencing on 29 cases. This study showed that gamma delta T-cell lymphoma arise from Vδ1 or Vδ2 cells dependent on the tissue compartment from which the lymphomas are derived. Genetic changes in gamma delta T-cell lymphoma are often in genes of the JAK-STAT, MAPK, MYC and chromatin signalling pathways.[34]

Especially, the studies from Torres[33] and Daniels[24] might indicate a shift away from targeted sequencing approaches towards whole-genome sequencing. This approach demands additional

### TABLE 2 Genomic analysis reveals deletion of JAK-STAT inhibitors in mycosis fungoides and several recurrently mutated genes crucial in pathogenesis pathways in Sézary syndrome, including Janus kinase (JAK)/signal transducers and activators of transcription (STAT), peroxisome proliferator-activated receptors (PPAR), PI3K-serine/threonine protein kinases (AKT) and fibroblast growth factor receptors (FGFR).

| Genomic analysis in mycosis fungoides[33] | A | B |
|---|---|---|
| Oncogenes upregulated | MALAT1, MECOM, PBX1, TTK, WWTR1 | ANK3, CAMSAP1, nC7orf42, CSMD1, DH11, FAT1, FLAD1, FLNB, FRAS1, GLUD2, GRIA2, PAPPA2, PCLO, PKHD1L1, UNC13C, VWA3B, XIRP2, LRP2, PABPC3 |
| Tumor suppressor genes downregulated | BRD7, CDKN1B, CYLD, HNRNPK, TSC1, XPA | GLU2, LRP2, PABPC3 |
| Developmental genes upregulation | GLI3, JAG1 | Mutated genes |
| Transcriptional repressor downregulated | FOXP1 | SOCS1, HNRNPK |
| Cell proliferation inhibitors downregulated | GPS2, RHOH | Most frequently mutated genes |
| Fusion transcripts | ATXN1-TP63, CCR7-DOT1L, KDM6A-IL1RAPL1, LMF1-TAF15, TP53-GPR3, YTHDF3-LIFR | GLU2, LRP2, PABPC3 |
| Recurrent deleted | SOCS1, HNRNPK | |
| Upregulation | NOTCH3 | |

### Sézary syndrome[32]

| Mutated genes | ANK3, CAMSAP1, nC7orf42, CSMD1, DH11, FAT1, FLAD1, FLNB, FRAS1, GLUD2, GRIA2, PAPPA2, PCLO, PKHD1L1, UNC13C, VWA3B, XIRP2, LRP2, |
| Most frequently mutated genes | GLU2, LRP2, PABPC3 |
resources in terms of funding, data processing and data storage but has distinct advantages. Whole-genome sequencing interrogates all regions of the genome equally (albeit low complexity region or regions containing repeats remain mostly inaccessible for short-read sequencing methods). This unbiased approach is superior to the hypothesis-based designs of targeted sequencing panels and therefor much more suited for complete elucidation of the genetic changes in one particular disease type. In addition, whole-genome sequencing leads to the potential detection of variations in non-coding regions. These mutations were neglected for a long time, but as shown in contemporary research (https://doi.org/10.1038/s41586-020-1965-x) these regions harbour highly recurrent mutations affecting gene expression and regulation. Furthermore, whole-genome sequencing enables identification of structural variations like deletions, amplifications or translocation with base-level precision. This is a distinct advantage over panel sequencing were amplifications, and deletions are only detected by aberrant coverage, and base-level localization of structural variation events is, in most cases, not achievable. This detection possibility from whole-genome sequencing is especially useful for CTCL with the high burden of copy number variations.

As already stated, predominantly heterogeneous molecular genetic alterations are found in CTCL. Nevertheless, the detection of specific molecular changes in known pathways enables considerations for targeted therapies.

Practical examples of this are alemtuzumab (humanized IgG1 kappa monoclonal antibody specific for CD52), Brentuximab (chimeric anti-CD30 monoclonal antibody conjugated to monomethyl auristatin E), mogamulizumab (humanized anti-CC chemokine receptor Type 4 monoclonal antibody) and IPH410lon (humanized that targets the immune receptor KIR3DL2/CD158k) [36-41].

Targeting CD47 is expressed on all normal cells, targets SIRPα on the surface of myeloid cells and may be a new cancer therapeutic strategy also in cutaneous T-cell lymphoma.

Inhibition of CD47-SIRPα via anti-CD 47 antibodies activates the innate immunity, promoting cancer cell destruction by macrophages. [42]

The phosphatidylinositol 3-kinase/AKT/mammalian target of rapamycin (PI3K/AKT/mTOR) signalling pathway regulates central aspects of cancer biology, such as metabolism, cellular growth and survival. In particular, a gain of function or hyperactivity of phosphoinositide 3-kinases (PI3Ks) has been demonstrated in several tumors. These enzymes are activated downstream tyrosine kinase receptors (RTKs) and/or G protein-coupled receptors (GPCRs) and, via AKT, are able to induce mammalian target of rapamycin (mTOR) stimulation. [43]

An upregulation of this pathway has been reported in CTCL [20]. Duvelisib is a promising new oral inhibitor of phosphatidylinositol 3-kinase (PI3K)-δ/γ isoforms currently in clinical development. PI3K-δ/γ inhibition may directly inhibit malignant T-cell growth, making duvelisib a promising candidate for patients with CTCL lymphoma [44].

Preliminary clinical data support a potential role of this drug in the treatment of CTCL. In a phase I open label study of duvelisib in...
patients with T-cell lymphoma, 19 CTCL patients were included with a response rate of 31.6%,[45] Figure 1.

4 | WHICH MAJOR OPEN QUESTIONS REMAIN TODAY?

One of the major basic questions is: How can an apparently innocent inflammatory lesion develop into a major life threatening disease as represented by advanced cutaneous T-cell lymphoma?

The complex interaction with initial mutagenic insult resulting in GCNAs but also SNVs, in selected genes involved with T-cell activation, epigenetic regulation and cell cycle regulation promote continued malignant cell survival and reduced apoptosis. So far, to our knowledge these mutations accumulate in the T-cell receptor, NFκB and JAK-STAT pathways resulting in continuous activation that promotes T-cell proliferation and inhibition of apoptosis. In addition, this process is further stimulated by skin resident pathogens, such as staphylococcus aureus. Targeting the bacterial load on the skin of CTLC patients has recently shown to be beneficial in advanced CTCL patients and might be an important addition to the therapeutic repertoire in the future.

It is further mandatory to understand the apparent T-cell activation pathway. It is known that genes, for example EB1, are driving T-cell maturation and differentiation. Mutations in the Bach2 locus are associated with multiple autoimmune diseases.[47] There are no published data for cutaneous T-cell lymphoma. This is an excellent example for the complexity in understanding the immunological behaviour of CTCL.[21,46]

One of the major questions is to elucidate recurrent mutations in mycosis fungoides (MF), concentrating on the most reported mutations in all published data or to elucidate recurrent patterns of mutated pathway in (MF).

Transcriptional programmes guiding lymphocyte differentiation depend on precise expression and transcription factors (TFs). For example, BACH2 is a TF essential for T and B lymphocyte maturation and differentiation. Mutations in the Bach2 locus are associated with multiple autoimmune diseases.[47] There are no published data for cutaneous T-cell lymphoma.

5 | WHICH CONCRETE EXPERIMENTAL APPROACHES SHOULD BE ADVOCATED TO PROVIDE THESE MISSING ANSWERS IN THE NEAR FUTURE?

Further sequencing studies of MF cases, where the study design is targeted towards answering the major open questions, like "Are there highly recurrent mutations in MF" or "Are there highly recurrent altered/mutated pathways in MF." To get a reliable data set for answering or ruling out one of the questions mentioned above, the study design and sample addition must be carefully evaluated.

On the side of the samples to be included in such a study, technical parameters as tumor cell fraction of the sample but also biological parameters as potential genetic alterations by preceding therapies must be considered. Sample collection and storage must be adapted to the respective subsequent application.

The methodical approach of this study should be a combined whole-genome/transcriptome sequencing approach with subsequent validation of, for example hyper-activated pathways by immunohistochemistry. Using this approach on a sufficient large set of carefully selected samples, it might be possible to draw connections between the genetic changes and the phenotypic changes in MF cells.

6 | OUR PERSONAL VISION ON HOW THIS LINE OF RESEARCH SHOULD BE DEVELOPED OVER THE NEXT DECADE AND WHY COULD THIS SUBSTANTIALLY CHANGE EXISTING PARADIGMS IN CLINICAL OR RESEARCH PRACTICE?

The above-mentioned approach of whole-genome/transcriptome sequencing of a large cohort of MF cases is only feasible in the near future as a collaboration project. Primarily collaboration must define important sample parameter criteria and provide sufficient methods for measuring/deriving these parameters. Afterwards, details for the experimental procedure, data generation, data storage and data analysis must be devised. After establishing, these important foundations on data generation analysis can be carried out. We see multiple advantages of such a collaboration. In the case of finding high recurrent genetic events, this study would further enhance our understanding of the molecular processes involved in MF and it might bring us one step closer to define important biomarkers.

In case that the data from the proposed collaboration of different lymphoma centre would not detect constant patterns of specific molecular changes in different patients, this study might also be of advantage in two aspects: (a) to further proof that MF is a complex genetically heterogeneous disease and (b) creates a necessary infrastructure to continue to analyse large genomic regions of MF patients to obtain single case genetic information for enrolment into precise targeted therapy studies. There is a high need to make high-throughput sequencing (HTS) available for personalized diagnostic in clinic daylife.

ACKNOWLEDGEMENTS
Open access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST
I herewith declare that I have no conflict of interest within the manuscript.
AUTHOR CONTRIBUTION
RS (first author) wrote the paper and analysed the data. CH contributed to writing the paper analysed the data and the figure. CC Analysed the data and contributed the necessary tools. RS contributed to writing the paper analysed the data and the figure. All authors have read and approved the final manuscript.

DATA AVAILABILITY STATEMENT
Data sharing not applicable to this article as no datasets were generated.

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