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A modern view of LGL leukemia

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Abstract:

Large granular lymphocytic (LGL) leukemia is a rare lymphoproliferative chronic disorder characterized by expansion of either T- or NK- cytotoxic cells. Contrary to EBV-induced aggressive NK-LGL leukemia, chronic T- and NK-LGL leukemia are indolent diseases affecting elderly patients with a median age of 66.5 years old. LGL leukemia is frequently associated with autoimmune disorders, most frequently rheumatoid arthritis. An auto/allo antigen is tentatively implicated in disease initiation. LGLs expansion is then triggered by proinflammatory cytokines such as interleukin (IL) IL-15, MIP-1, and RANTES. This proinflammatory environment contributes to deregulation of proliferative and apoptotic pathways. Following the initial description of the JAK-STAT pathway signaling activation in the majority of patients, recurrent STAT3 gain of function mutations have been reported. The JAK-STAT pathway plays a key role in LGL pathogenesis by promoting survival, proliferation and cytotoxicity. Several recent advances have been made towards understanding the molecular landscapes of T and NK LGL leukemia, identifying multiple recurrent mutations affecting the epigenome, such as TET2 or KMT2D, and crosstalk with the immune microenvironment, such as CCL22. Despite an indolent course, published series suggest that the majority of patients will eventually need treatment. However, it is noteworthy that many patients may have a long-term observation period without ever requiring therapy. Treatments rely upon immunosuppressive drugs, namely cyclophosphamide, methotrexate and cyclosporine. Recent advances have led to the development of targeted approaches, including JAK-STAT inhibitors, cytokine targeting and hypomethylating agents, opening new developments in a still-incurable disease.

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A modern view of LGL leukemia

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Author contribution

TM, TPL and TL wrote and approved this manuscript.

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37 aggressive NK-LGL leukemia, chronic T- and NK-LGL leukemia are indolent diseases affecting
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44 majority of patients, recurrent *STAT3* gain of function mutations have been reported. The
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46 and cytotoxicity. Several recent advances have been made towards understanding the
47 molecular landscapes of T and NK LGL leukemia, identifying multiple recurrent mutations
48 affecting the epigenome, such as *TET2* or *KMT2D*, and crosstalk with the immune
49 microenvironment, such as *CCL22*. Despite an indolent course, published series suggest that
50 the majority of patients will eventually need treatment. However, it is noteworthy that many
51 patients may have a long-term observation period without ever requiring therapy.
52 Treatments rely upon immunosuppressive drugs, namely cyclophosphamide, methotrexate
53 and cyclosporine. Recent advances have led to the development of targeted approaches,
54 including JAK-STAT inhibitors, cytokine targeting and hypomethylating agents, opening new
55 developments in a still-incurable disease.

56

57 **Introduction**

58 Large granular lymphocytic leukemia (LGLL) is a rare hematological malignancy characterized
59 by clonal expansion of cytotoxic T cells leading to diverse clinical and biological
60 manifestations. LGLL accounts for 2-5% of chronic lymphoproliferative disorders with an
61 estimated incidence of 0.2-0.72 cases per million population/year.¹ LGLL can be divided into
62 2 entities according to phenotype, namely T- and NK-LGLL, accounting for 85% and 15% of
63 cases respectively, and sharing a common pathophysiology and presentation.² With an
64 estimated 10-years overall survival (OS) of above 70% in T-LGLL and 65% in NK-LGLL, LGLL is

65 an indolent disease.²⁻⁴ However, about half of patients will eventually need treatment
66 because of symptomatic cytopenias or associated autoimmune manifestations. Infections
67 represent the main cause of death.

68 The clonal nature of the disease was proved in 1985 and the description of the T and NK
69 entities was made in 1993.^{5,6} The discovery of JAK-STAT pathway deregulation and the later
70 identification of recurrent STAT3 mutations in both T-LGL and NK-LGLL represented a key step
71 in the understanding of the pathophysiology and unified the two entities.⁷ T-LGL and
72 aggressive NK-LGLL were included in the World Health Organization (WHO) classification in
73 2001 in the “Mature T- and NK-cell neoplasms” group. Until recently, NK-LGL proliferation
74 was considered a “provisional entity” because of difficulties demonstrating clonality.
75 Therefore, the term “Chronic Lymphoproliferative Disorder of Natural Killer Cells” (CLPD-NK)
76 was used, opposed to the aggressive natural killer leukemia (ANKL). Thanks to the
77 identification of recurrent mutations in clonal NK lymphoproliferations, the last 2022 WHO
78 classification included both T- and NK-LGL leukemia.⁸ By contrast, the 2022 International
79 Consensus Classification (ICC) kept the T-LGL and CLPD-NK denominations.⁹

80 This review will cover pathogenesis of the disease, clinico-biological features, diagnostic
81 workflows, and treatment recommendations, including future directions.

82

83 **Pathophysiology**

84 After initial expansion, thought to be due to a chronic antigen stimulation, persistence of
85 monoclonal LGLs is the consequence of resistance to the Fas-induced apoptosis, a pro-
86 inflammatory cytokine environment, activation of the JAK-STAT pathway and epigenetic
87 alterations (**Figure 1**).

88

89 **Initiating event**

90 LGLs clones commonly display an effector memory phenotype suggesting the involvement of
91 chronic stimulation by an auto/allo antigen in leukemogenesis, further supported by peculiar
92 associations with autoimmune disorders and documented interactions between LGLs and
93 dendritic cells.¹⁰ Several viral pathogens, including HTLV1/2 and EBV, have been suspected
94 despite no documented evidence of direct viral DNA insertion.¹¹⁻¹³ Interestingly,
95 hematological responses to antiviral therapies have been observed in LGLL infected patients

96 (HCV, HBV and HIV).^{14 15} Importantly, no common TRA or TRB clonotype shared by different
97 patients was identified in single cell analyses coupled with TCR profiling.^{16,17} However, in
98 most patients, LGL clones shared a TCR target with their normal counterpart. While the
99 triggering event may likely be a result of different antigens, it would appear that the
100 mechanisms sustaining pathogenesis are common and may be independent of the inciting
101 antigen.

102

103 **The role of inflammatory cytokines in LGL expansion**

104 In LGLL, sustained LGLs expansion is favored by several cytokines, including interleukin-15 (IL-
105 15), IL-18, IP10 (CXCL10), and platelet derived growth factor.¹⁸⁻²¹ Deregulation of cytokine
106 production leads to a pro-inflammatory microenvironment, contributing to LGL
107 pathophysiology (**Figure 2**).²² LGLs clones secrete high levels of cytokines and their cognate
108 receptors forming an autocrine loop activating survival and proliferations pathways.^{20,23,24} IL-
109 15 plays a crucial role in the genesis and homeostasis of NK- or T-LGL: mice lacking the IL-15 α
110 receptor display an NK-cell and CD8^{pos} memory T cell defect.²⁵ Interleukin-15 is
111 overexpressed by LGLs leukemic clones and *in-vitro* culture of LGLs isolated from patients are
112 IL-15 dependent.²⁶ In addition, transgenic mice overexpressing IL-15 develop either T- or NK-
113 LGLL.²⁷ Finally, IL-15 chronic *in-vitro* exposure leads to a leukemic transformation due to IL-
114 15-induced centrosome aberration and DNA hypermethylation. Interleukin-6 could be
115 implicated in LGLL pathogenesis as high levels of IL-6, produced in part by non-leukemic
116 clones, were observed in some LGL-leukemia patients.^{28,29}

117

118 **Resistance to the Fas-induced apoptosis**

119 Physiologically, pathogen clearing is followed by activation of the Fas-mediated activation-
120 induced cell death. LGL clones are characterized by resistance to Fas-induced apoptosis,
121 almost always without evidence of FAS gene mutation as observed in ALPS syndrome.³⁰⁻³²
122 FAS-L overexpression in LGL clones leads to secretion of soluble Fas (sFas) acting as a decoy-
123 receptor inhibiting Fas-dependent apoptosis.³¹ Moreover, in LGLL, increased expression of
124 the inhibiting C-FLIP molecule, downstream to the Fas-receptor, leads to decreased caspase 8
125 cleavage and ultimately inhibits the death induced signaling complex (DISC).³³

126

127 **The Genetic landscape of LGL leukemia**

128 Since the discovery of constitutive activation of STAT3 in 2001 as the hallmark of LGLL,
129 several mutations affect key T-cell cellular functions, such as cytokine secretion, proliferation,
130 apoptosis and epigenetics.^{7,34,35} As observed in the vast majority of hematological
131 malignancies, LGLL is characterized by a clonal heterogeneity with the cooccurrence of
132 different mutations (**Figure 3**).³²

133

134 **a) A key role of JAK-STAT signaling**

135 The JAK/STAT pathway plays a major role in the regulation of T-cells. The role of STAT3 in LGLL
136 was identified in 2001 with high levels of phosphorylated STAT3.³⁵ STAT3 inhibition using an
137 antisense oligonucleotide restored Fas-dependent apoptosis. *STAT3* gain-of-function
138 mutations were later identified in T- and NK-LGLL, unifying both entities.^{7,36} *STAT3* mutations
139 are identified in up to 60% of T-LGLL and 30% of NK-LGLL.^{37,38} *STAT3* mutations are classically
140 missense mutations found in the region encoding for the Src homology 2 domain (SH2) with
141 the D661Y and Y640F mutations accounting for 80% of all mutations found.³⁶ These
142 mutations induced constitutive dimerization and phosphorylation of STAT3, leading to
143 increased transcription of antiapoptotic genes (*BCLXL*, *FLIP*), cell cycle genes (*CDKN1D*,
144 *CMYC*) and proinflammatory cytokine coding genes (IL-6, IL-12, IL-17, IL-21, IL10 and IFN γ).
145 Multiple *STAT3* mutations can be found in LGLL patients, supporting the existence of
146 subclonal evolution as observed in acute leukemia.³⁹ *STAT3* gain-of-function mutation leads
147 to a more cytotoxic profile, higher blood LGL level, and deeper cytopenia. It is associated
148 with an hypermethylated status, a higher expression of FASL and an increased ROS
149 level.^{16,29,40} Interestingly, *STAT3* gain-of-function mutations are described in several
150 autoimmune diseases associated with a CD8^{pos} T-cell expansion.⁴¹ In a mouse model, *STAT3*
151 gain-of-function induced expansion of NKG2D^{pos}CD8^{pos}CD62L^{neg}CD44^{pos} T-cells and
152 overexpression of cell cycle and killer cell genes (*GZMA* and *GZMB*) through NKG2D/IL2-IL15
153 receptor interactions.⁴² While current opinion states autoimmune disease and LGLL can both
154 arise from a common pro-inflammatory context, this study demonstrate that the LGL clone
155 itself may play a crucial role in auto-immunity development. In addition to *STAT3*, *STAT5B*
156 mutations have been reported in LGLL patients, particularly in T $\gamma\delta$ -LGLL (6%) or in the rare
157 indolent form of CD4^{pos} T $\alpha\beta$ -LGLL (45%).^{40,43-46} Mutations of other genes implicated in the

158 JAK-STAT pathway, such as *JAK1*, *JAK3*, *IL6R*, *PTPRT*, and *GNAS* have also been described.^{32,47}
159 The JAK/STAT pathway can also be activated by non-mutational mechanisms, such as
160 cytokine modulation and epigenetic inactivation of JAK-STAT pathway inhibitors, including
161 micro RNAs (miRNA) modifications. miR-181a and miR-146b have been associated with
162 STAT3 activation in unmutated-patients.^{48,49} Finally, deregulation of other signaling pathways
163 (i.e. MAP-kinase, PI3K/AKT or NF-KB) is reported in LGLL inducing pro-survival signals.⁵⁰⁻⁵²
164 Accordingly, NRAS, KRAS, PI3KCD and TNFAIP3 mutations complete the genomic landscape of
165 LGLL.

166

167 **b) Mutations affecting epigenetic pathways**

168 Epigenetic modifications are recent developments in understanding LGLL pathophysiology.
169 DNA methylation alteration seems to be a crucial event in NK-LGLL development, as
170 suggested by the high frequency of *TET2* (Ten-eleven-translocation 2) mutations in this LGLL
171 subtype. Initially described in few cases of LGLL, we recently reported that *TET2* mutations
172 are present in 28 to 34% of NK-LGLL patients.^{38,53} However, *TET2* mutations are also reported
173 in clonal hematopoiesis of indeterminate potential (CHIP) affecting the myeloid
174 compartment but not normal T-cells.⁵⁴ *TET2* mutations have been initially described in
175 myeloid disorders, aplastic anemia and also in various T-cell malignancies, including angio-
176 immunoblastic lymphoma.^{55,56} Most recently, clonal hematopoeisis was reported in some
177 LGL leukemia patients with neutropenia, with *TET2* mutation seen in a small percentage.⁵⁷ In
178 myelodysplastic syndromes, *TET2* mutations are associated with hypermethylation of genes
179 implicated in NK-cell function including Killer Immunoglobulin-like receptors (KIR), perforin,
180 and *TNFA*.⁵⁸ In NK-LGLL, *TET2* mutations were associated with a methylation pattern distinct
181 from normal NK cells, including the hypermethylation of *PTPRD* (a negative regulator of
182 *STAT3*) and the JAK inhibitor *SOCS3*, all contributing to the activation of the JAK-STAT
183 pathway.^{38,53,59} We explored the clonal hierarchy of genomic alterations in NK-LGLL. In some
184 cases, *TET2* can occur early and be shared between NK-cell and myeloid compartments. In
185 this case, *TET2* can explain the link between NK-LGLL and the development of other *TET2*-
186 derived malignancies, such as MDS. *TET2* may support the selection of NK-cell clones which
187 can secondarily acquire *STAT3* mutations leading to the cytotoxic phenotype, and ultimately
188 define a symptomatic NK-LGLL. This hypothesis is supported by the co-occurrence of *TET2*
189 and *STAT3* or *CCL2* in a third of *TET2* mutated cases. *TET2* can also be restricted to NK-cell

190 clones and support *STAT3* activation through epigenetic silencing of JAK-STAT regulators.
191 *TET2* seems to be a crucial event in NK-LGLL development, presenting relevant clinical
192 features, such as more thrombopenia and frequent associations with other malignancies. In
193 T-LGLL, mutations of the histone monomethyl-transferase *KMT2D* are detected in up to 20%
194 of cases.³² The exact role of *KMT2D* in LGLL pathogenesis remains unclear, but chromatin
195 accessibility profiling can discriminate LGLL from others mature T-cell malignancies.⁶⁰ Clearly,
196 epigenetic modifications constitute a new field in LGLL pathophysiology, which should be
197 elucidated with single cell analyses and functional studies, detailed later.

198

199 **c) Role of the immune microenvironment**

200 Mutations affecting the *CCL22* encoding gene are observed in 27% of NK-LGLL.⁶¹ *CCL22*
201 mutations were enriched at highly conserved residues and mutually exclusive of *STAT3*
202 mutations. They consist of *gain of function* alterations, inducing a CCR4 internalization defect
203 in targeted cells, leading to increased cellular chemotaxis and dysregulated crosstalk with the
204 hematopoietic microenvironment. For example, myeloid cells and dendritic cells produce
205 higher IL-15 level in vitro with mutated *CCL22*, which may favor NK-cell proliferation.
206 Similarly, a recent study reported that *STAT3*-mutated patients display skewed Th17/Treg
207 ratios and abnormal distributions of monocyte populations with increases in intermediate
208 and non-classical monocytes.⁶² *CCL5*, a cytokine produced by LGL clones induced high-level
209 of IL-6 release by monocytes. Further studies are needed to gain mechanistic insight and to
210 test potential therapeutic intervention targeting this dysregulated crosstalk.

211

212 **Clinico-biological features**

213

214 With a median age of 66.5 years old, LGLL usually affects elderly people with similar
215 incidence in men and women. Symptomatology is dominated by neutropenia-related
216 infections which represent the highest risk of mortality. The main clinico-biological features
217 reported in the literature are summarized in **Table 1**.

218

219 **Clinical manifestations**

220 Clinical manifestations vary largely among the LGL patients' population. Neutropenia-related
221 infections affect 15-39% of patients and involve the skin, oropharynx, perirectal area and the
222 lungs. Life-threatening bloodstream infections may occur. Opportunistic bacterial, fungal and
223 viral infections are uncommon. Some patients have prolonged neutropenia without any
224 infection. Splenomegaly is seen in 20-50% of cases while hepatomegaly and
225 lymphadenopathy are less common. Fatigue and B symptoms are observed in 20-30% of
226 cases. Tissue infiltrations of the skin, nerves or kidney have been described sporadically.⁶³⁻⁶⁵
227 As opposed with indolent LGLL, aggressive NK LGLL is characterized by systematic bone
228 marrow and organ involvement, marked deterioration of the general status and an extremely
229 poor OS.⁶⁶ In this context, the diagnosis of hepato-splenic T cell lymphoma (generally
230 CD4^{neg}CD8^{neg}CD56^{pos}) must be also ruled out.⁶⁷
231 LGLL is at the interface between hematology and autoimmunity, with autoimmune disorders
232 reported in ~25-32% of cases.^{68,69} Several autoimmune disorders have been described,
233 mostly in case reports and small cohorts. Rheumatoid arthritis (RA) represents the main
234 autoimmune disorder associated with LGLL, affecting 10-15% of patients and is usually
235 diagnosed before or concomitantly to the LGLL. Sjogren syndrome, rhizomelic pseudo
236 polyarthritits and unclassified inflammatory arthritits have also been described.^{2,70-72} Psoriasis
237 incidence seems to be preferentially observed in patients carrying the CCL22 mutation.⁶¹
238 Pulmonary artery hypertension has also been described.⁷³ Vasculitits such as
239 cryoglobulinemia, cutaneous leukocytoclastic angiitits and ANCA-negative microscopic
240 polyangiitits have been reported. The regression of vasculitits-related manifestations following
241 the treatment of LGL-leukemia highlights the close relationship between the two
242 conditions.⁷⁴ Occasionally, systemic lupus erythematosus and inclusion body myositis have
243 been reported.
244 Solid cancers and hematological malignancies are found in 5 - 21% of LGLL patients.^{2,71}
245 Monoclonal gammopathy of undetermined significance, multiple myeloma and B-cell
246 lymphomas have been reported.⁷⁵ Overrepresentation of cancers in LGLL patients is difficult
247 to ascertain due to its high incidence above the age of 60 years.
248 STAT3 mutations are associated with a more symptomatic phenotype with a higher incidence
249 of neutropenia, associated autoimmune disorders including RA, a more frequent treatment
250 requirement and a reduced OS.^{76,77} More specifically, STAT3 mutation D661Y is correlated
251 with the presence of macrocytic anemia.¹⁸

252

253 **Biological features**

254 Neutropenia is observed in 70-85% of cases with a higher incidence in T-LGLL compared to its
255 NK counterpart.² Fas-mediated apoptosis has been implicated in the pathogenesis of
256 neutropenia. Fas-ligand, produced in excess by LGLs clones, binds to the neutrophils Fas-
257 receptors inducing apoptosis.⁷⁸ Moreover, auto-antibodies are found in 20-40% of patients
258 and can form immune-complexes binding to the fc receptors of neutrophils. Anemia is
259 usually moderate and less than 10-20% of patients are transfusion-dependent. Conversely,
260 anemia is the most frequent cytopenia in Asia, affecting 29-42% of LGL patients mainly due
261 to pure red cell aplasia (PRCA). Hemolytic anemia and immune thrombocytopenia have
262 occasionally been reported.⁷⁹ Thrombocytopenia, usually moderate, is observed in 19% of
263 patients. Bone marrow involvement, observed in 70% - 90% of cases, is unlikely to directly
264 contribute to cytopenias as infiltration is subtle in the majority of patients. Lymphocytosis is
265 inconstant and LGL threshold was lowered to $0.5 \times 10^9/L$ even if the $2 \times 10^9/L$ threshold is
266 still retained as a diagnostic criterion in the last 2022 ICC and WHO classifications.^{8,9,80}
267 Indeed, authentic LGLL are described with a circulating LGL count between 0.5 and $2 \times 10^9/L$.
268 Serum electrophoresis frequently shows hypergammaglobulinemia. Antinuclear antibodies
269 are seen in 20%. Increased β_2 microglobulin and sFas-L are seen in 65% and 95%
270 respectively.

271 $T\gamma\delta$ LGLL variant represents only 5% of all T-LGLL. Even if $T\gamma\delta$ and $T\alpha\beta$ entities share clinical
272 and biological features including STAT3/5B mutations, the frequencies of cytopenia is higher
273 in $T\gamma\delta$ subtypes and survival lower than $T\alpha\beta$ LGLL.^{4,81,82} Recent whole-exome sequencing
274 data found shared somatic mutations and putative drivers between $T\alpha\beta$ -LGL and $T\gamma\delta$ -LGLL.³²

275

276 **The CD4^{pos} T-LGLL: a rare entity with a specific presentation and outcome.**

277 Alongside with the largely predominant CD3^{pos}CD8^{pos} T-LGLL phenotype, a rare
278 CD3^{pos}CD4^{pos}CD8^{neg} entity has been reported.⁸³ Compared with classical CD8^{pos} T-LGLL,
279 patients with a CD4^{pos} T-LGLL seem to have a more indolent evolution with less cytopenia
280 and autoimmune manifestations. A higher incidence of associated neoplasia such as
281 monoclonal B-cell lymphocytosis and plasma cell disorders has been reported.^{83,84} CD4^{pos} T-
282 LGLL are characterized by a high frequency of STAT5B mutation.⁴³ In the rare CD4^{pos} T-Cell

283 LGLL, the diagnosis of prolymphocytic leukemia, sharing similarities in term of phenotype
284 and molecular profile, should be ruled out.^{45,83}

285

286 **Diagnosis**

287 In a compatible clinico-biological context, the aim of diagnostic procedures is to distinguish
288 between reactive LGL expansion and LGLL. Reactive polyclonal LGL expansion can be seen in
289 various situations, such as viral infections (CMV, EBV, HIV, etc.), after splenectomy, and organ
290 or stem cell transplantation.^{85,86} A polyclonal LGL expansion has also been described in
291 association with hematological malignancies and autoimmune conditions.⁸⁷

292 Therefore, diagnosis is based on 2 mandatory criteria: (1) the identification of an elevated
293 number ($> 0,5 \times 10^9/L$) circulating LGL cells based on the complete blood cell count and/or
294 compatible phenotypic pattern and (2) a proof of clonality obtained by flow cytometry
295 and/or molecular biology. The diagnosis workflow is presented in **Figure 4**.

296

297 **Cytology**

298 Large granular lymphocytes are easily identified on a blood smear. These large cells (15-
299 20 μ m) are characterized by abundant cytoplasm containing azurophilic granules and a
300 reniform or round nucleus with mature chromatin. In a normal setting, LGLs represent 10-
301 15% of mononuclear cells i.e., 0,21 – 0,29 LGL $\times 10^9/L$. Leukemic and normal LGLs are
302 morphologically indistinguishable, justifying phenotypic analyses when LGLL is suspected.
303 Caution is needed in the case of normal lymphocyte count. Blood analyses are usually
304 sufficient to ascertain the diagnosis and bone marrow exploration is only recommended in
305 atypical presentations or in case of associated confounding conditions such as PRCA or MDS.
306 This exploration is particularly useful in patients with low ($<1 \times 10^9/L$) LGL count to confirm
307 the diagnosis.

308 Bone marrow involvement, observed in the vast majority of patients, is frequently subtle
309 without any correlation between the degree of LGL marrow infiltration and the severity of
310 cytopenia. Histological analysis classically shows intra-sinusoidal linear clusters of LGLs.⁸⁸
311 LGLs are in most cases CD8^{pos} Granzyme B^{pos} and TiA1^{pos}.

312

313 **Clonality assessment**

314 LGLL has a CD3^{pos} T phenotype in 85% of diagnoses whereas its CD3^{neg}CD56^{pos}/CD16^{pos} NK
315 counterpart represents 15% of cases. In most cases, leukemic T-LGLs display a terminal
316 effector memory T-cell phenotype (TCRαβ^{pos}CD45^{pos}D8^{pos}CD57^{pos}CD16^{pos}CD62L^{neg}) and an
317 aberrant dim expression of CD5.⁸⁹ TCRγδ LGLs with a CD4^{neg}CD8^{neg} phenotype are seen in
318 about 15% of cases.⁸¹ The proof of clonality is a key step in the diagnosis of T-LGLL. TCR Vβ
319 analysis by flow cytometry can be used as a surrogate marker of TCR clonality with
320 commercially available antibodies covering ~ 70% of the Vβ repertoire. However, clonal
321 rearrangement of TCRγ gene by polymerase chain reaction (PCR) using primers targeting
322 conserved region of the VDJ segments remains the gold standard.^{90,91} In TCRαβ^{pos} LGLL, flow
323 cytometry-based analysis of the constant region 1 of the TCRβ chain (TCRBC1) has been
324 recently developed with high sensitivity and good correlation with the TCR sequencing.^{92,93}
325 However, this procedure is neither widely available and its high sensitivity could lead to the
326 identification of T-cell clones in patients not meeting LGL-diagnostic criteria or corresponding
327 to the T-cell clone of undetermined significant (T-CUS) entity.⁹⁴ Similarly, clonality can be
328 assessed by deep sequencing of the TCR repertoire in highly specialized laboratories.⁴⁴
329 Normal NK cells can be divided into 2 main phenotypes based on the expression of CD16 and
330 CD56. Indeed, CD56^{low}CD16^{high} NK-cells are mainly characterized by their cytotoxic properties
331 whereas CD56^{high}CD16^{low} NK-cells are cytokine producing cells.^{95,96} In NK-LGLL, leukemic cells
332 usually display the following phenotype:
333 CD2^{pos}sCD3^{neg}CD3ε^{pos}TCRαβ^{neg}CD4^{neg}CD8^{pos}CD16^{high}CD56^{low}. However, phenotypic analysis
334 does not allow easily the distinction between normal and leukemic NK cells. Compared with
335 T-LGLL, proof of clonality is far more difficult to obtain in chronic NK cells LGL since NK T cells
336 do not express TCR. A restricted KIR repertoire has been used as a surrogate marker of
337 clonality.^{97,98} Similarly to T-LGLL, recurrent mutations have been recently described in the NK
338 entity with *STAT3*, *TET2* and *CCL22* mutations observed in around 30% each.^{38,53,61} In order
339 to distinguish authentic NK-LGLL from reactive NK-cell proliferation, we recently proposed a
340 NK clonality score combining KIR repertoire analysis by flow cytometry and molecular
341 analysis.³⁸

342

343 **How we treat LGL leukemia**

344 LGLL remains an indolent but incurable disease, with a reported 10 years OS above 70% in
345 the largest retrospective studies.^{2,3,70,71} Treatment indication and strategy do not differ
346 between T- and NK-LGLL. First line treatment still relies on immunosuppressive drugs (**Figure**
347 **5**). Recent advances in our understanding of pathogenesis have opened the way to the
348 development of new therapeutic approaches targeting the IL-15 signaling, JAK-STAT
349 pathways and epigenetic deregulation.

350

351 **When do we treat?**

352 Consistent with the indolent evolution, a watch and wait strategy can be proposed in nearly
353 half of the cases but only 20% will not need treatment in their lifetime. Severe neutropenia
354 (neutrophils < 0,5 X 10⁹/L), neutropenia-related infections, transfused-dependent and
355 symptomatic anemia represent the main indications. Auto-immune disorders represent an
356 indication of treatment in 12% of cases in our experience.² Evaluation of the treatment
357 response is mostly based on the blood parameters and transfusion dependency. The role for
358 minimal residual disease detection using flow cytometry or molecular approaches remains to
359 be determined.

360

361 **First line treatment**

362 Single agent cyclophosphamide, methotrexate and cyclosporine are the 3 recommended
363 drugs in first line. No consensus exists regarding the treatment sequence.^{2,3,70,99,100} Overall
364 response rates (ORR) reported with the 3 available drugs range from 38-75% depending on
365 the retrospective or prospective nature of the studies.^{2,3,37,70,99,101,102} Only 2 prospective
366 studies have been conducted in naïve patients. The ECOG study reported an ORR of 38%
367 after methotrexate.¹⁰¹ 160 patients have been enrolled in the prospective randomized study
368 comparing cyclophosphamide and methotrexate in France (NCT01976182).³⁷ Results of the
369 interim analysis performed on the first 96 patients showed an ORR to the first line of 55% at
370 4 months with only 16% complete remission and a high rate of relapse occurring in 67% of
371 the cohort. Methotrexate (10mg/m²/week) and cyclosporine A (3mg/kg/day) are generally
372 given until progression whereas cyclophosphamide should not be given more than 1 year
373 because of the mutagenic risk. Treatment response is assessed after a minimum of 4 months.
374 Cyclophosphamide or cyclosporine may be more adapted for patients with anemia,

375 especially PRCA. Methotrexate is appropriate in patients with RA because of its activity in
376 both conditions. In the absence of response to one drug, a switch is recommended.
377 Cyclophosphamide and methotrexate are generally considered as the best first line option.
378 Cyclosporine A is usually considered for LGLL patients with overlapping aplastic anemia as
379 well as patients failing both drugs. A recent retrospective study including 60 patients in
380 second line reported a 70% ORR with cyclophosphamide. By contrast, methotrexate was not
381 effective in patients failing cyclophosphamide.¹⁰³

382

383 **Treatment in relapsed/refractory diseases**

384 Several approaches have been evaluated in patient refractory to the 3 main
385 immunosuppressives drugs. Alemtuzumab have been used with promising results (56% ORR;
386 95% CI 35-76) but high toxicity (7 deaths out of 25 patients).¹⁰⁴ Bendamustine and purine
387 analogues such as fludarabine and cladribine have shown interesting response rates in small
388 retrospective studies.^{100,105} In LGLL patients with aplastic anemia, antithymocyte globulins
389 associated or not with cyclosporine A led to some responses.⁷⁰ Autologous and allogeneic
390 stem cell transplantations have been rarely used in highly pretreated and refractory
391 patients.¹⁰⁶

392 Given the key role of JAK-STAT pathway in the pathogenesis of LGLL, JAK inhibitors such as
393 ruxolitinib represent an attractive option. We initially reported the efficacy of ruxolitinib in 2
394 patients with refractory T-LGLL.¹⁰⁷ The efficacy of ruxolitinib was recently confirmed in a
395 prospective phase 2 clinical trial.^{108,109} In 20 patients with refractory/relapsed LGLL evaluable,
396 the ORR and complete response rate were respectively 55% and 30%. Interestingly, STAT3
397 mutational status was predictive of the event free survival (EFS) with a 14-month EFS of
398 100% in the mutated patients compared with 40% in the non-mutated patients. We
399 confirmed these impressive results in a series of 21 refractory/relapsed patients with an 85%
400 ORR.¹¹⁰ These results lead us to consider ruxolitinib as one of the best 2nd line options.
401 Similarly, tofacitinib, a JAK3 inhibitor demonstrated partial efficacy in LGLL patients with
402 associated RA but yet with a significant toxicity.¹¹¹

403

404 **Future therapeutic directions**

405 BNZ-1, a pegylated peptide selectively inhibiting the binding of IL-15 and other γ c cytokines
406 to their receptors has been recently prospectively evaluated in a phase 1/2 clinical trial after
407 promising preclinical results.^{112,113} In 20 highly pretreated patients, 20% had an objective
408 clinical response. Futures studies are warranted to confirm the efficacy of this agent as a
409 monotherapy or in combination. A phase I study evaluating siltuximab is ongoing
410 (NCT05316116). Azacitidine, an hypomethylating agent, inhibits STAT3 activation by SHP1
411 restoration and DNMT1 downregulation.²⁹ A phase I study with oral azacitidine is ongoing
412 (NCT05141682). Efficacy of decitabine was reported in a refractory patient.¹¹⁴ A phase I/II
413 trial assessing the safety and efficacy of DR-01, a non-fucosylated antibody targeting the
414 CD94 lectin receptor is now recruiting (NCT05475925). Similarly, ABC008 is a first-in-class
415 monoclonal antibody targeting the co-inhibitory T cell receptor killer cell lectin-like receptor
416 G1 (KLRG1). A phase I/II trial is ongoing in the United States (NCT05532722). Specific STAT
417 inhibitors have been developed. KT-333 is a STAT3 degrader currently evaluated in a phase
418 Ia/Ib study (NCT05225584). Drugs targeting IL-6 and its receptor such as tocilizumab and
419 siltuximab could also represent potential candidates. Considering the multiple pathways
420 involved in the pathogenesis of LGLL and the clonal heterogeneity of the disease, it is
421 conceivable that a multidrug approach combining a JAK-STAT inhibitor and a cytokine
422 targeting agent may be efficient based on a personalized therapy approach.

423

424 **Innovative research strategies**

425 There remain several research areas in need of additional study to enhance our
426 understanding of LGL leukemia pathogenesis and clinical management. Multiple recent
427 studies have defined the somatic variants in coding genes as well as transcriptomic profiles
428 for large cohorts of T- and NK-LGL leukemia patient samples^{32,38,53,61}. Thus, the field must
429 now fully characterize the functional consequences of recurrent molecular events, the
430 impact of co-occurring somatic variants, and the contribution of mutant acquisition
431 sequence to LGL biology. Refined studies are needed to define the biochemical, molecular,
432 and clinical consequences for the large list of *STAT3* somatic variants that have been reported
433 in LGL leukemia.

434

435 Further single-cell transcriptomic analyses with associated definitions of T-cell receptor
436 clonality have refined our understanding of LGL-specific gene expression programs and

437 pathways.^{16,17} Knowledge gaps include a lack of single-cell transcriptomics for NK-LGL
438 leukemia, integrated single-cell chromatin accessibility and gene expression data, and
439 detailed analyses of samples with varying mutational status in *STAT3*, *TET2*, *CCL22* and other
440 recurrently mutated genes. New insights will be gained by comparing LGL single-cell datasets
441 to those acquired from T-cells during acute or chronic viral infection as well as tumor
442 infiltration. New spatial transcriptomics platforms also provide the opportunity to explore
443 single-cell gene expression along with tissue localization and cell-cell communication of LGLs
444 in the context of bone marrow or other tissue microenvironments relevant to disease
445 symptoms and progression.

446

447 Beyond somatic variants and gene expression, the field lacks a detailed catalog of chromatin
448 accessibility, DNA methylation, histone modifications, long-range enhancer interactions,
449 transcription factor networks, large-scale duplications and deletions, and the impact of non-
450 coding variants on these parameters. *STAT3* variants are linked to co-mutation of chromatin
451 and epigenetic modifier genes, thus a full picture of the genomic architecture of LGL
452 leukemia requires that each of these datatypes be acquired and integrated in samples of
453 varying *STAT3* mutational subtypes. Finally, each of these technologies should be applied to
454 longitudinal samples that span the course of disease progression and treatment to
455 characterize molecular events associated with clonal evolution, clinical features and
456 treatment response. The refined molecular characterization provided by these new datasets,
457 especially single-cell and spatial transcriptomics studies, is likely to yield new LGL-specific
458 therapeutic targets and strategies.

459 **Conclusion**

460 LGLL is a rare lymphoproliferative disorder characterized by large spectrum of clinico-
461 biological manifestations and a peculiar association with auto-immune disorders. Even
462 though single agent immunosuppressive drugs induce responses in the majority of patients,
463 relapses are frequent and the disease remains incurable. Advances in the understanding of
464 the pathophysiology with the identification of recurrent mutations open the way to the
465 development of new therapeutic strategies.

466

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Table 1.

Parameters	Loughran et al. (1993)	Semenzato et al. (1997)	Bareau et al. (2010)	Sanikommu et al. (2017)	Zhu et al. (2020)	Dong et al. (2021)
Number of patients	129	162	229	204	108	319
T-LGL leukemia (%)	100	100	88	90	100	93
NK-LGL leukemia (%)	NA (aggressive form)		12	10	0	8
Median age (year) [min-max]	57 [15-88]	59	59 [12-87]	63 [54-72]	51 [21-78]	65 [17-90]
Sex ratio (M/F)	0,8	0,8	0,8	0,9	0,9	0,9
Biological features						
LGL count (G/L)	NA	NA	37%<1G/L, 15%>4G/L	1,7 [0,8-3,3]	2,07 [0,3-45,5]	0,9 [0,5-2,3]
Median neutrophil count [min-max]	NA	NA	NA	1,56 [0,8-2,6]	1,36 [0,04-9,6]	NA
Neutropenia (%) (ANC < 1,5G/L)	84	NA	59	46	57	41
Severe neutropenia (ANC < 0,5G/L) (%)	48	37	24	17	10	17
Median Hb level [min-max]	NA	NA	NA	11,7 [10-13]	7,5 [3,1-15,6]	NA
Anemia (%)	49	26	24	40	59	41
Transfusion dependency (%)	NA	NA	6	22	58	19
Thrombocytopenia (%)	19	9	17	30	8	26
Antinuclear antibodies	38	38	17	NA	45	22
Rhumatoid factor (%)	57	43	14	NA	10	39
STAT3 mutation (%)	NA	NA	NA	36	28	40*
Clinical manifestations						

Treatment requirement	73	33	44	58	97	57
B symptoms (%)	NA	26	7	NA	0	63
Hepatomegaly (%)	23	32	10	NA	6	NA
Splenomegaly (%)	50	44	24	24	41	28
Lymphadenopathies (%)	1	12	6	NA	7	NA
Recurrent infections (%)	39	61	22	NA	12	NA
Autoimmune manifestations (%)	28	NA	32	25	23	26
Rheumatoid Arthritis (%)	28	NA	17	15	2,7	12
Other hematological malignancies (%)	NA	NA	10	19	0	19
Solid tumor (%)	NA	NA	4	17	0	21
LGL related death (%)	36	NA	7	5	3	NA

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795

796 **Figures legends**

797 **Figure 1.** LGL leukemia pathogenesis: polyclonal LGLs expansion is thought to be initiated by
798 a viral/autoantigen. LGLs expansion is then sustained by inflammatory cytokines whose can
799 also contribute to the frequently associated autoimmune disorders. LGLs expansion and
800 clonal selection can also be favored by the occurrence of specific mutations including STAT3
801 and CCL22 inducing a resistance to apoptosis, increased proliferative capacities and
802 dysregulation of the crosstalk with the immune microenvironment respectively. Even in the
803 absence of STAT3 mutation, the JAK-STAT pathway is activated in the majority of LGL
804 leukemia patients. Epigenetic modifications have also been described with TET2 mutations,
805 possibly representing an early event, observed in ~ 30% of cases. Production of inflammatory
806 cytokines and release of the cytotoxic granules by the leukemic LGLs in the infiltrated tissues
807 lead to a spectrum of clinical and biological manifestations including cytopenia, fatigue and
808 autoimmune diseases. Abbreviations: LGL: large granular lymphocytic leukemia. IL:
809 interleukin, PDGF: Platelet-Derived Growth Factor, TET2: Ten-eleven-translocation 2, CCL22:
810 C-C Motif Chemokine Ligand 22, STAT3: Signal transducer and activator of transcription 3,
811 FasL: Fas Ligand, IP10 (CXCL10): Interferon gamma-induced protein 10, TRAIL: tumor-
812 necrosis-factor related apoptosis inducing ligand.

813

814 **Figure 2.** Main deregulated pathways in LGL leukemia: Deregulation of apoptosis pathways is
815 a key element in LGL leukemia pathogenesis. LGLs clones are resistant to the Fas-mediated

816 apoptosis. Secreted soluble Fas (sFas) act as a decoy of FasL preventing the formation of the
817 Fas-mediated death-inducing signaling complex (DISC). Apoptosis cascade is also inhibited by
818 an increased level of an inhibitory protein named cellular FADD-like IL-1 converting enzyme
819 inhibitory protein (c-FLIP). Ras and phosphoinositide 3-kinase (PI3K) / protein kinase B (AKT)
820 pathways are also activated in LGL leukemia and contribute to the apoptosis inhibition. The
821 JAK-STAT pathway is constitutively activated in LGL leukemia and leads to the transcription of
822 B-cell lymphoma 2 (BCL-2) and myeloid cell leukemia 1 (Mcl-1) antiapoptotic proteins
823 expression. Indeed, the JAK-STAT pathway is activated by several mechanisms. Gain of
824 function STAT3 mutations are observed in 30-60% of patients and have recently been shown
825 to trigger the expansion of cytotoxic LGL cells expressing high level of NKG2D. The JAK-STAT
826 pathway is also activated downstream to the cytokine's receptors. Increased secretion of
827 inflammatory cytokines creates an autocrine loop. Mutations affecting genes implicated in
828 epigenetic mechanisms such as Ten-eleven-translocation 2 (TET2) and lysine
829 methyltransferase 2D (KMT2D) have been recently described. Gain of function CCL22
830 mutation induce a defect in its CCR4 receptor internalization leading to an increase adhesion
831 of myeloid and dendritic cells. These immune cells can stimulate LGL cells survival and
832 proliferation in part by IL-15 secretion. Inflammatory cytokines secretion and cytotoxic
833 granules release lead to the clinical symptoms and biological features observed in LGL
834 leukemia.

835

836 **Figure 3.** Mutational landscape of LGL leukemia. (A) Clinico-mutational correlation. STAT3,
837 STAT5B and TET2 mutations have been associated with specific clinico-biological features. *
838 Compared to STAT3 wildtype. **CCL22 and STAT3 mutations are mutually exclusive. (B)
839 mutational landscape of LGL leukemia (N=120 patients). Courtesy from Dr Cédric Pastoret,
840 hematology department, Rennes university hospital. Abbreviations: AITL:
841 Angioimmunoblastic T-cell lymphoma, MDS: myelodysplastic syndrome, CMML: chronic
842 myelomonocytic leukemia, Ref: references.

843

844 **Figure 4.** Diagnosis algorithm of LGL Leukemia. * NK clonality score based on 4 parameters:
845 NK cell count > $11 \times 10^9/L$: 2 points / KIR restricted phenotype: 2 points / CD94 or NKG2A^{hi}: 1
846 points / STAT3, STAT5B, TET2 or TNFAIP3 mutation: 2 points.³⁸

847

848 **Figure 5.** Treatment algorithm in LGL Leukemia

849

850 **Table 1.** Clinical and biologic presentation: data from the largest retrospective series.

851 Abbreviation: M: male, F: female, NA: not available, ANC: absolute neutrophils count. *

852 Performed only on 25 patients

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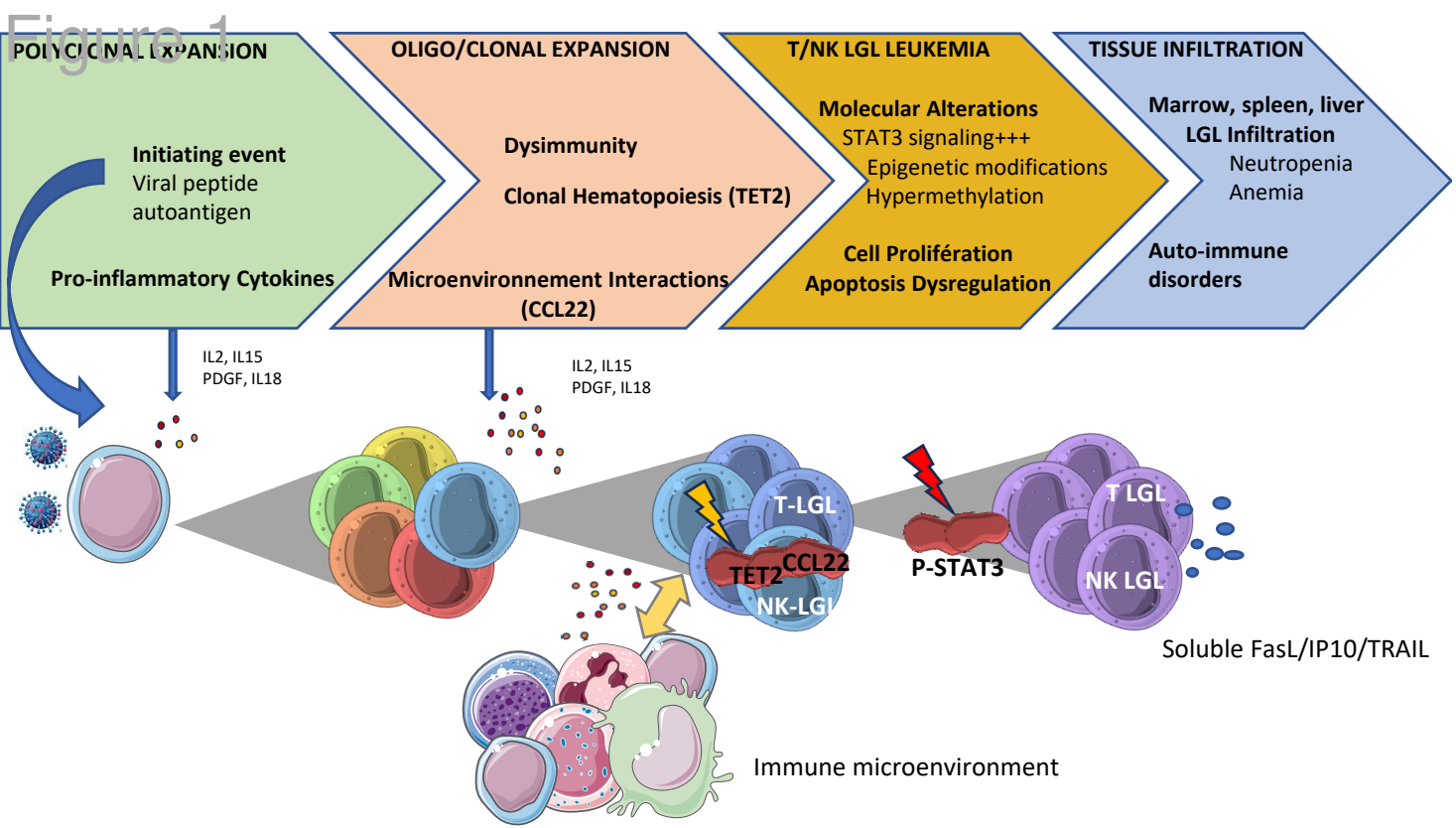


Figure 1

Figure 2

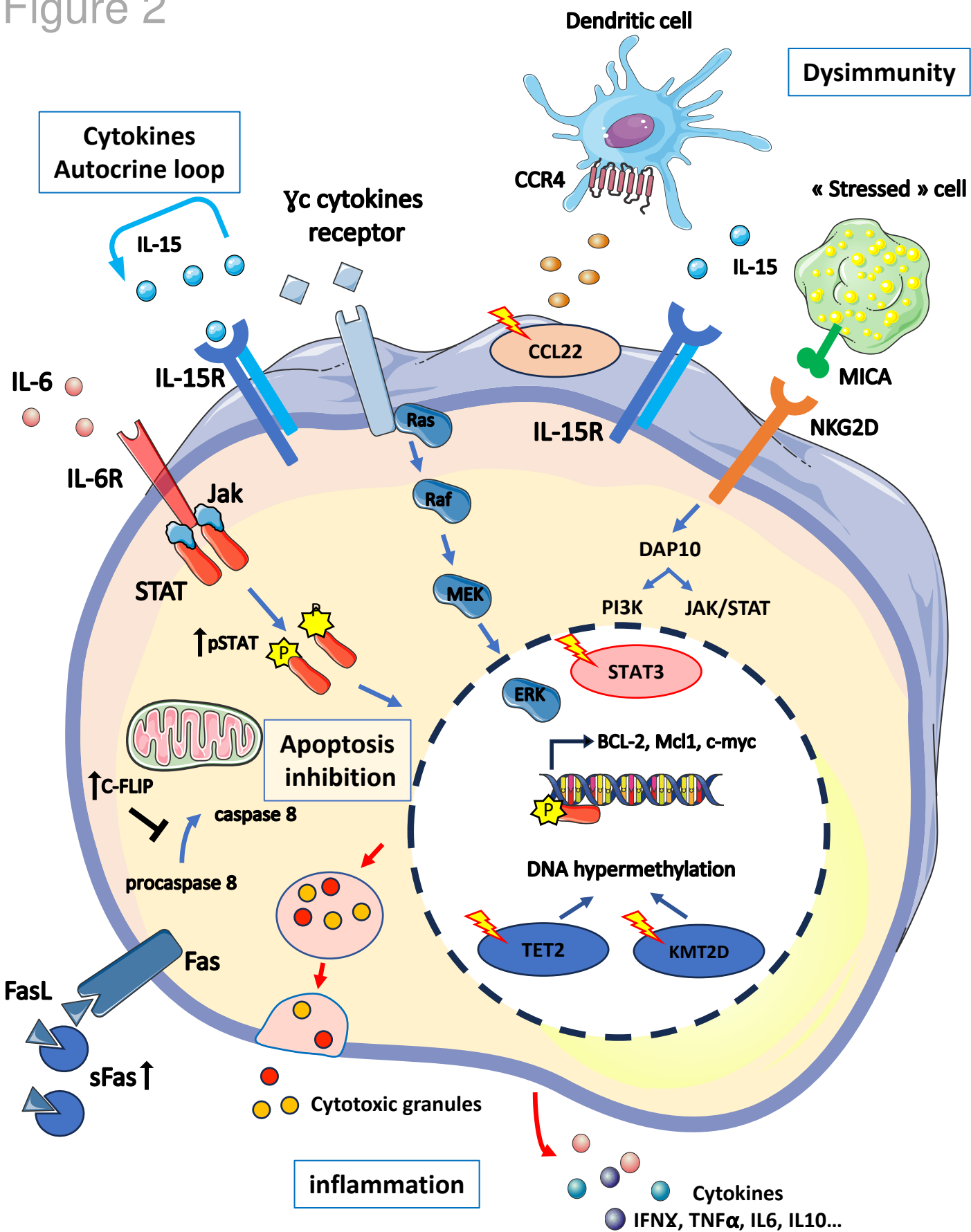


Figure 2

Figure 3

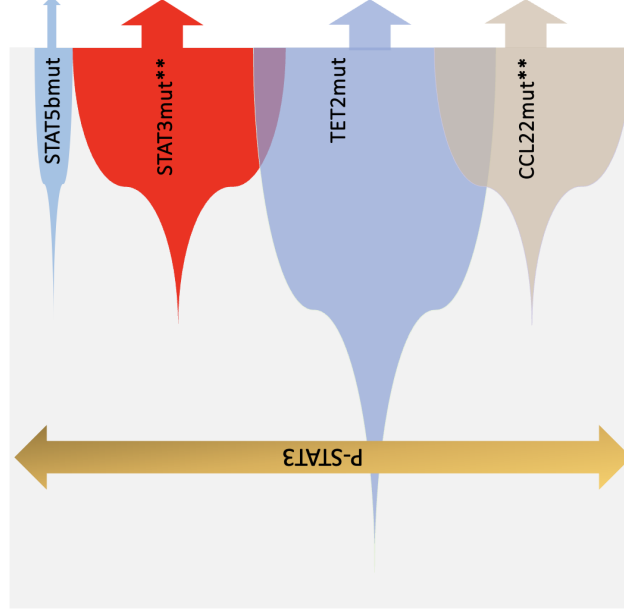


Figure 3

*as compared to STAT3wt

** CCL22 and STAT3 mutations mutually exclusive

B

T-LGLL (85%)		NK-LGLL (15%)	Ref
<5%	<ul style="list-style-type: none"> 45% CD4^{pos} T subtype < 5% of CD8^{pos} subtype 	<2%	40,43, 46
50-70%	<ul style="list-style-type: none"> Lower granulocyte count* Lower survival* 	25-35%	32,36
8%	?	<ul style="list-style-type: none"> CD16^{low} Lower platelet count AITL-like gene expression Association with hematologic disorders (MDS, CMML) 	38,53
<1%	?	<ul style="list-style-type: none"> CD56^{high} CD16^{dim} 	61

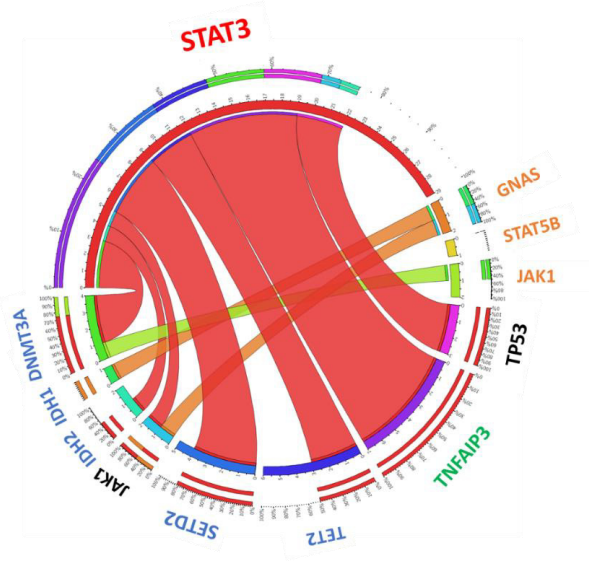


Figure 4

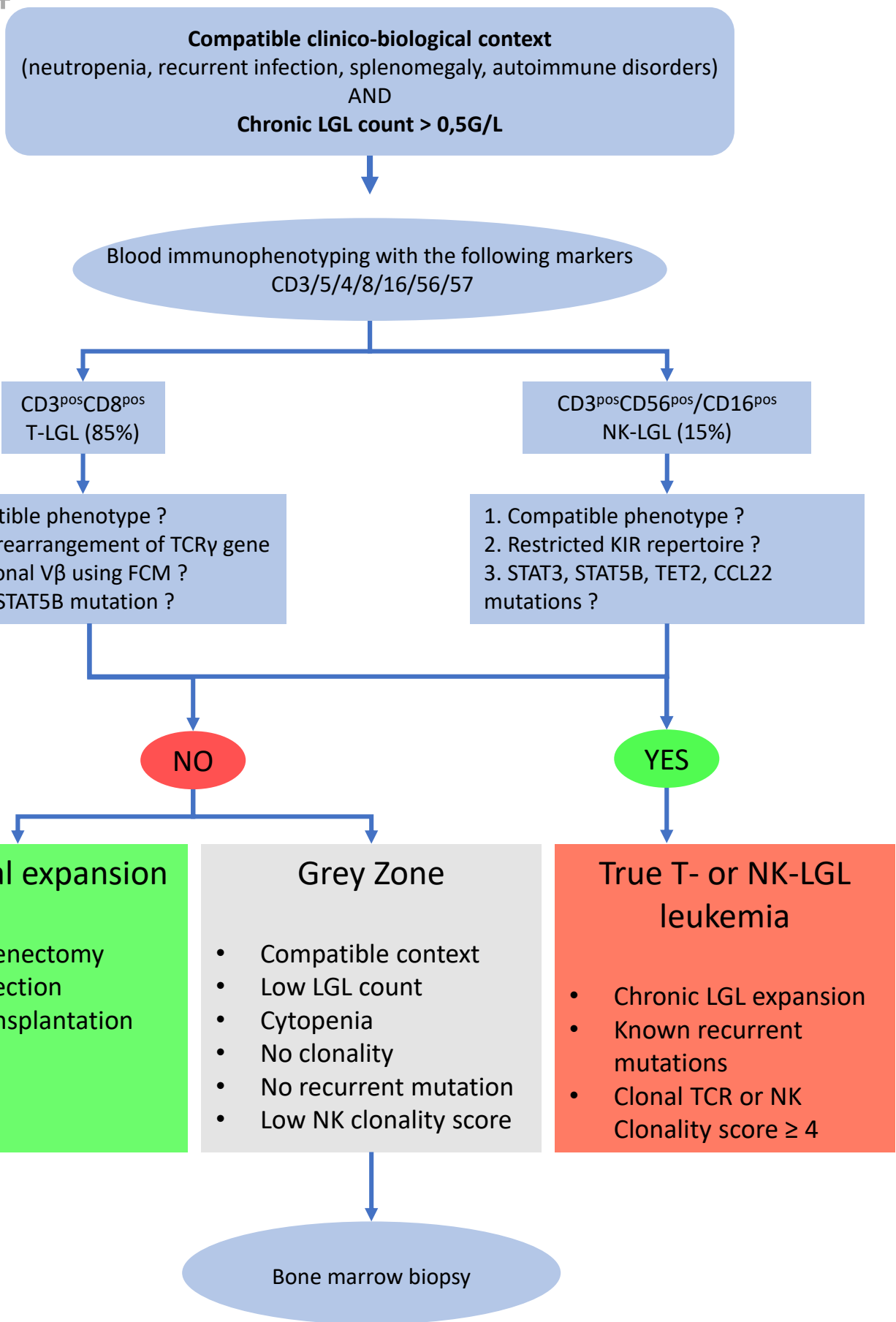


Figure 4

Figure 5

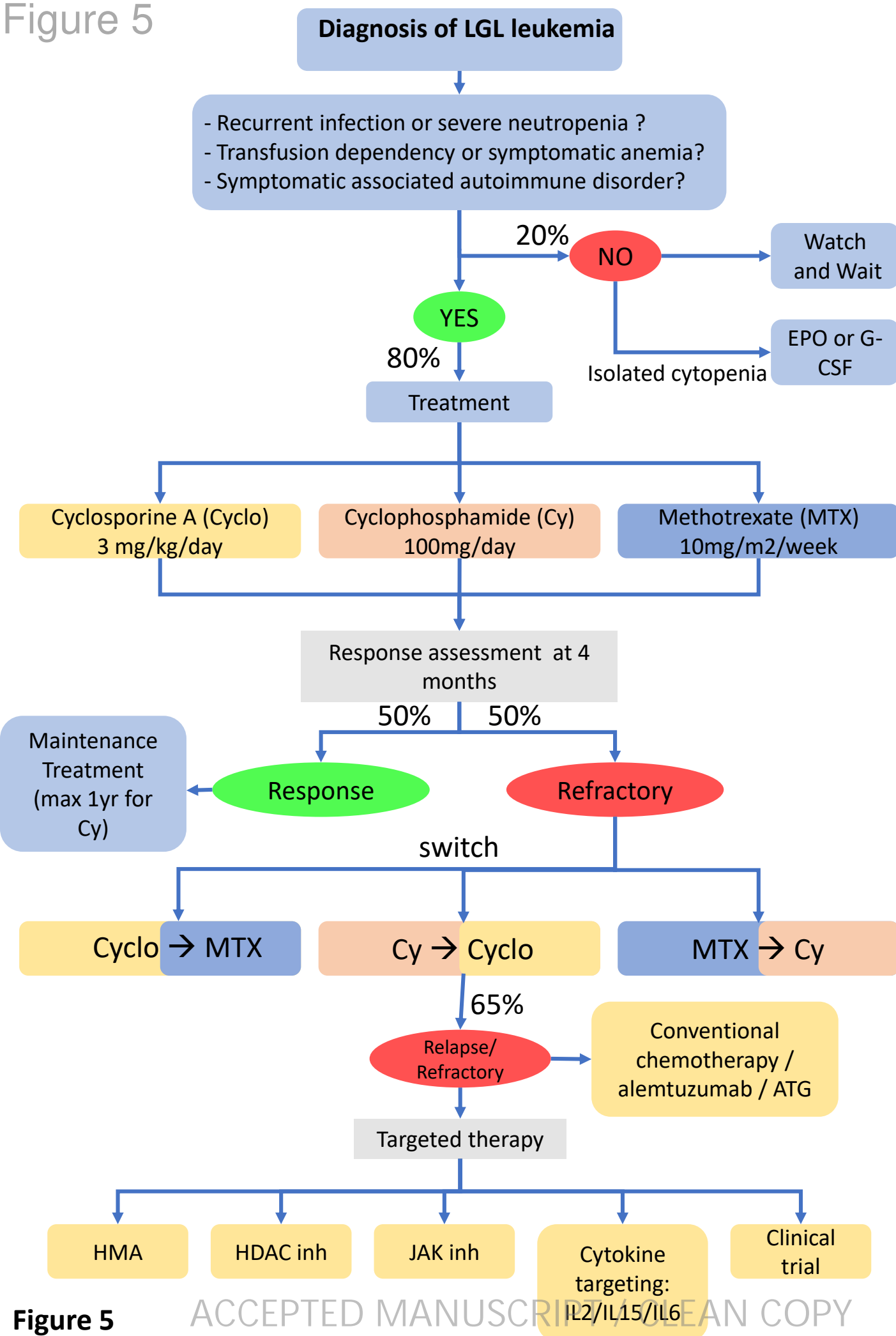
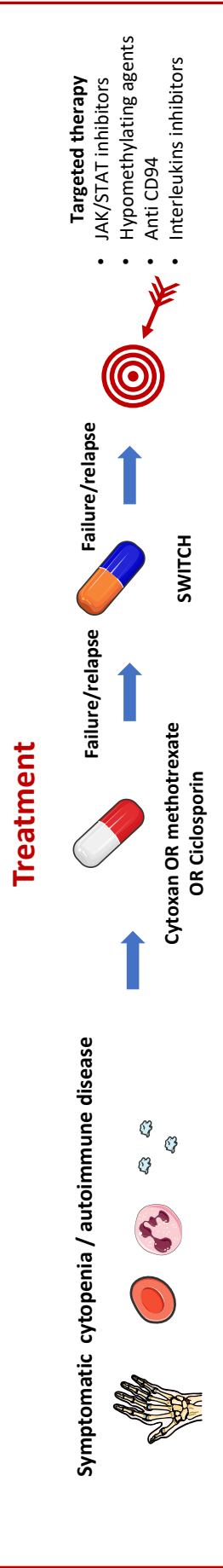
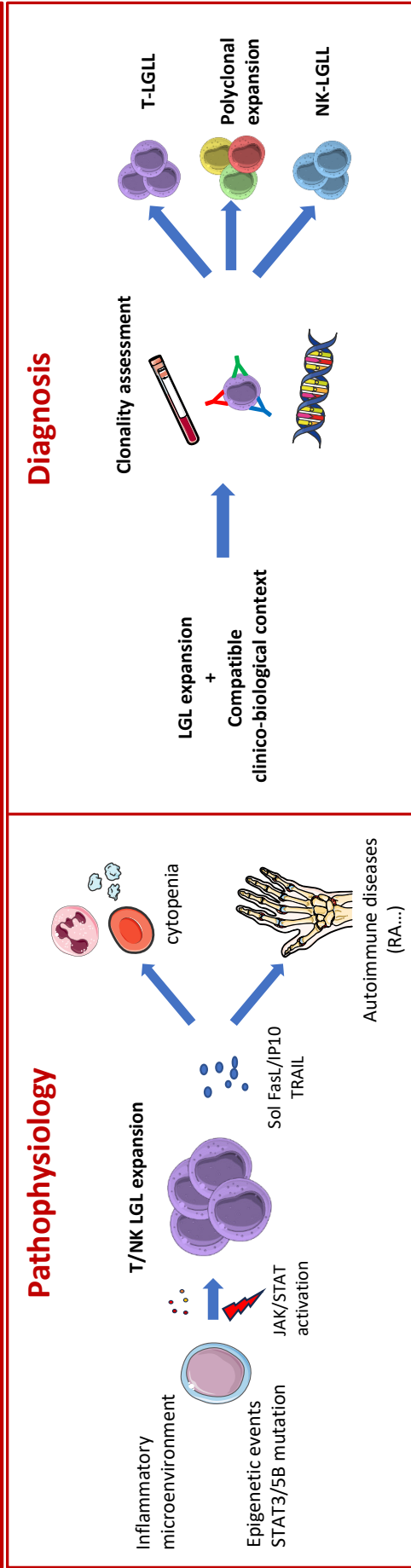


Figure 5

Large Granular Lymphocytic (LGL) Leukemia: Updates in the Pathophysiology, Diagnosis and Treatment



Conclusions: LGL leukemia is a rare chronic lymphoproliferative disorder characterized by an expansion of cytotoxic T or NK lymphocytes. Improvement in our understanding of the genetic landscape opens the way to the development of new targeted therapeutic strategies.

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