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GLUCOCORTICOID RECEPTOR ISOFORM SWITCHING UNDER EXOGENOUS STEROID PRESSURE: A HIDDEN DRIVER OF STEROID RESISTANCE

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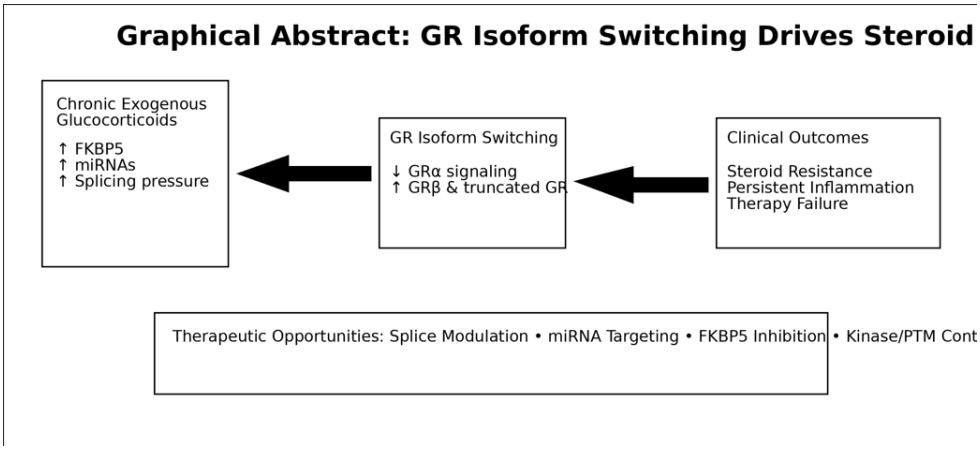
ABSTRACT

Steroid resistance undermines the therapeutic utility of glucocorticoids (GCs) across many diseases (asthma, inflammatory bowel disease, some cancers, sepsis and hematologic malignancies). One increasingly recognized mechanism is *isoform switching* of the glucocorticoid receptor (GR; NR3C1), where the relative complement of receptor isoforms — generated by alternative splicing, alternative translation initiation and post-translational modification — shifts in response to sustained/exogenous GC exposure and other environmental pressures. Here we synthesize molecular, cellular and clinical evidence that isoform switching (notably increased expression or activity of GRβ and selected translational isoforms) contributes to loss of GC responsiveness, outline the mechanisms that drive switching (splicing factors, miRNAs, feedback via chaperones/co-chaperones and PTMs), and discuss clinical contexts, therapeutic implications and testable hypotheses. We include a literature-derived summary table and an illustrative chart of the balance of supporting studies. This review emphasizes that monitoring and therapeutically targeting GR isoform balance may reclaim steroid sensitivity in refractory patients.



INTRODUCTION

Glucocorticoids (GCs) are cornerstone anti-inflammatory and immunosuppressive drugs used across specialties. Their effects are mediated largely through the glucocorticoid receptor (GR, gene NR3C1), a ligand-activated transcription factor that controls gene programs governing inflammation, metabolism and cell survival [1–3]. Still, a clinically important fraction of patients exhibits partial or complete resistance to GCs, or acquire resistance after prolonged therapy [4–6]. Multiple mechanisms contribute to steroid resistance (genetic mutations/deletions in NR3C1, altered GR expression/localization, increased expression of GC-resistant isoforms, disturbed chaperone/co-factor regulation, post-translational modifications, microRNAs and epigenetic changes) [7–12]. Among these, isoform switching — changes in the relative abundance or activity of GR isoforms such as GRα, GRβ, GRγ and translational variants — is a plausible and under-appreciated driver of clinical resistance under exogenous steroid pressure [2,3,9,13–16].

This paper reviews the evidence linking isoform switching to steroid resistance, proposes molecular mechanisms by which exogenous GC exposure selects or induces GR isoform shifts, summarizes clinical correlations, and outlines translational strategies to detect and reverse clinically relevant switching.

Biology of GR isoforms — a brief primer

NR3C1 produces multiple receptor proteins by (a) alternative splicing of exon 9 to yield GRα and GRβ, (b) alternative translation initiation producing N-terminally truncated translational isoforms (GR-A, GR-B, GR-C1–3 etc.), and (c) post-translational modification (phosphorylation, acetylation, ubiquitination, sumoylation) that alters activity and stability [2,3,13–15,17]. GRα is the canonical, ligand-binding receptor that mediates most classical GC actions. GRβ is produced by alternative splicing replacing exon 9α with exon 9β; it does not bind classic GCs and was classically described as a dominant-negative inhibitor of GRα in some contexts [8,13,18]. However, GRβ also has intrinsic GRα-independent activities (transcriptional regulation, promotion of migration/proliferation in some cancers), complicating its role [14,19–21]. Translation-initiated isoforms differ in their N-terminal AF-1 domain length and show distinct transcriptional activities and subcellular localization [3,15,22].

Site-specific phosphorylation (e.g., S203, S211, S226) modulates GR transcriptional activation in a gene- and context-dependent way [23–26], and co-chaperones (FKBP5/FKBP51) and HSP90 regulate GR folding, ligand binding and nuclear translocation — importantly, FKBP5 is itself GC-responsive, forming an ultra-short negative feedback loop [10,27]. MicroRNAs (miR-124, miR-144, others) and epigenetic modifications (promoter methylation, histone marks) regulate GR mRNA levels and splicing choices [11,28–30].

Mechanisms by which exogenous steroid pressure can drive isoform switching

Sustained exogenous GC exposure imposes a selection and regulatory pressure on GR signalling networks. Mechanisms plausibly linking exogenous GCs to isoform switching include:

1. **Altered alternative splicing**: Hormone-responsive splicing factors and promoter usage can change after prolonged GC exposure, altering exon 9 usage and increasing GRβ transcripts in some contexts [13,31]. Inflammatory cytokines and TGF-β can also influence splicing factor expression, feeding into isoform balance [32,33].
2. **Feedback regulation via induced co-factors**: GC induction of FKBP5 and other chaperone/co-chaperone proteins reduces GRα ligand affinity and nuclear translocation, functionally mimicking reduced GRα signaling despite unchanged GRα mRNA — this altered activation state may favor cellular programs that upregulate GRβ or translational isoforms as compensation. FKBP5 upregulation is a well described GC-induced feedback loop. [10,16,27]
3. **MicroRNA-mediated repression of GRα**: GC-induced or inflammation-induced miRNAs (e.g., miR-124, miR-144) can target GRα or regulatory sequences influencing GRβ stability/translation, shifting the effective GRα:GRβ ratio [11,19,28,34]. For example, miR-124 downregulates GRα in liver failure models associated with GC resistance [11]; miR-144 action on GRβ 3′UTR was implicated in bladder cancer migration experiments [19].
4. **Post-translational modification and selective stabilization**: Chronic GC exposure can change GR phosphorylation patterns (S211/S226) or ubiquitination that alter isoform stability and activity. Some translational isoforms are differentially susceptible to PTMs; altered PTMs can thus favor isoforms with less transactivation capacity [23–26,35].
5. **Selection for resistant clones (somatic mutation/deletion)**: In proliferative disorders (leukaemia), prolonged GC therapy can select for clones with NR3C1 mutations or deletions, or with alternative splicing favouring non-functional isoforms; these genetic/epigenetic changes often co-exist with isoform shifts [9,12,36].
6. **GRβ intrinsic activity and paracrine/autocrine loops**: GRβ's intrinsic regulation of inflammatory genes in a GRα-independent manner can create feed-forward inflammatory states that blunt GC responses and further select for GRβ-dominant signalling [14,21].

   Together, these mechanisms form a multi-layered process in which exogenous GCs not only select but induce regulatory circuits that alter GR isoform expression and function, producing diminished clinical responsiveness.

Clinical evidence linking isoform switching and steroid resistance

Steroid-resistant airway disease (asthma, nasal polyps, COPD)

Multiple studies reported elevated GRβ mRNA or altered GRα:GRβ ratios in steroid-insensitive asthma and nasal polyps; however, some clinical studies find inconsistent correlations depending on tissue sampled and detection method [4,7,18,37–39]. Pujols and colleagues summarized early evidence associating increased GRβ with steroid-

insensitive asthma and airway disease [4,7]. Not all cohorts replicated a simple relationship in peripheral blood lymphocytes, indicating tissue specificity [37].

Inflammatory bowel disease (ulcerative colitis)
Increased GRβ expression has been reported in steroid-refractory ulcerative colitis samples and nasal polyp tissue, consistent with a role for isoform switching contributing to local steroid refractoriness [4,40].

Hematologic malignancies (ALL and other leukaemia's)
GC-induced apoptosis is central to treatment of childhood acute lymphoblastic leukaemia (ALL), and GR signalling defects are a major cause of therapeutic resistance. Recurrent alterations in NR3C1 (mutations, deletions) and altered isoform expression correlate with poor prednisone response and relapse [9,12,36,41–43]. Some datasets show GRγ or translational isoform patterns associate with in vitro GC resistance [15,42].

Cancer (breast, bladder, other solid tumours)
GR isoform expression patterns affect proliferation, migration and therapy response in several cancers. GRβ can promote migration in bladder and breast cancer models and attenuate apoptosis [19,21,44]. In some tumour contexts, GR activation paradoxically promotes tumour progression; isoform balance appears key to these divergent effects [21,44–46].

Sepsis, critical illness and liver disease
In critical illness and sepsis, dynamic changes in GR signalling — including isoform expression and miRNA regulation (e.g., miR-124) — contribute to variable responses to systemic corticosteroids observed in trials [11,47–49].
A concise *literature-summary table* is provided below (Table 1). The table lists representative clinical/experimental studies that link isoform expression or switching with steroid resistance or altered GC responses.

Table 1. Representative studies linking GR isoform expression/switching with steroid resistance (selected examples)

Study (year)	Disease / model	Sample / system	Key finding
Oakley et al., 1999 [8]	in vitro models	cell lines	Demonstrated GRβ dominant-negative activity against GRα
Pujols et al., 2003/2007 [4,37]	Asthma, airway disease	airway tissue	Reported increased GRβ or altered GRα:GRβ in steroid-insensitive asthma
Kino et al., 2009 [13]	Review / molecular	Multiple	Described mechanisms of GRβ generation and functions
Haarman et al., 2004 [15]	ALL	leukemic samples	GRγ associated with in vitro GC resistance in some cases

Study (year)	Disease / model	Sample / system	Key finding
Liu et al., 2021 [12]	Pediatric ALL	genomic analysis	NR3C1 mutations/deletions associated with GC resistance
Ramos-Ramírez et al., 2021 [14]	Review	multiple	GRβ intrinsic activities and contribution to inflammation
Wang et al., 2020 [11]	ACLF (human)	liver failure samples	miR-124 downregulates GRα — linked to GC resistance
McBeth et al., 2016 [19]	Bladder cancer (in vitro)	cell lines	GRβ increases migration; miR-144 regulates GRβ
Bender et al., 2013 [17]	Translational isoforms (cells)	cell models	GR translational isoforms mediate distinct GC responses
Tamai et al., 2022 [36]	BCP-ALL	exome sequencing	NR3C1 mutations confer GC resistance
Hasan et al., 2024 [2]	Review/meta-analysis	multiple	Overexpression of GRβ associated with steroid-resistant diseases
Lockett et al., 2024 [1]	Review	multiple	Updated review of GR isoforms in sensitivity/resistance
Chen et al., 2008 [23]	Molecular	cell lines	Phosphorylation at S211/S226 affects target gene expression
Binder, 2009 [10]	Review	FKBP5	FKBP5 feedback loop modulates GR sensitivity
Others (see refs)	Various	Various	Supporting and nuance studies

An integrative mechanistic model

Under chronic/exogenous GC exposure, cells enact compensatory responses: GC-induction of FKBP5 and other regulators diminishes GRα activity; inflammation or cellular stress alters splicing factor expression; miRNAs modulate GRα or GRβ transcripts; and selective PTMs change isoform stability. Collectively, these effects can (1) reduce effective GRα activity, (2) raise relative GRβ abundance, and (3) promote expression of translational isoforms with lower transactivation. GRβ itself can promote pro-inflammatory or pro-survival gene expression in certain contexts, creating a feed-forward loop of resistance (Figure 1). In proliferative disorders, clonal selection and somatic NR3C1 mutations further entrench resistance [9,12,36]. This model predicts that (a) tissue-specific monitoring of GRα:GRβ and translational isoform ratios will better predict GC responsiveness than total NR3C1 mRNA alone, and (b) interventions targeting splicing, miRNA regulation, FKBP5 or PTM enzymes could restore sensitivity.

Therapeutic and diagnostic implications

Diagnostic biomarker strategies

1. **Isoform-specific assays**: Quantitative PCR assays that distinguish exon-9 isoforms (9α vs 9β) and measures of translational isoforms (by targeted

proteomics) in disease-relevant tissues should be developed and validated as predictive biomarkers of response [13,15,37]. Peripheral blood measurements may be insufficient for tissue-restricted diseases [37].

2. **Composite biomarker panels**: Combine GRα:GRβ ratio, FKBP5 expression, phosphorylation pattern (S211/S226), and relevant miRNAs (miR-124, miR-144) to better predict GC sensitivity.

Therapeutic directions

1. **Splicing modulators**: Small molecules or antisense oligonucleotides to reduce GRβ splicing or shift splicing toward GRα may restore sensitivity in tissues where GRβ drives resistance [13,31]. Precedent: splice-switching oligos in other diseases.
2. **miRNA antagonists**: AntagomiRs against miRNAs that suppress GRα (e.g., miR-124) or that upregulate GRβ (miR-144 in specific cancers) could rebalance isoform expression [11,19].
3. **Targeting FKBP5**: Small molecule FKBP5 inhibitors could relieve FKBP5-mediated GR insensitivity; FKBP5 inhibition has shown phenotype effects in preclinical stress models [10,16].
4. **PTM enzyme inhibitors**: Modulating kinases (p38, JNK) that phosphorylate GR (S211/S226) could tune GR activation and apoptotic responses in leukaemia's or inflammatory cells [23,24,26].
5. **Combination strategies in leukaemia**: For GC-resistant ALL with NR3C1 alteration or isoform switching, combine BCL2 pathway inhibitors or agents that bypass GC-dependence with isoform-targeting strategies [36,41,42].

Limitations, open questions and priorities for future research

1. **Causality vs association**: Many human studies report associations between GRβ expression and steroid resistance, but causal proof in vivo remains limited. Controlled manipulation of isoforms in disease-relevant animal models will be decisive [14,19].
2. **Tissue specificity**: Peripheral blood measures often do not reflect tissue isoform balance. Disease-site biopsies or single-cell approaches are needed to resolve heterogeneity [37].
3. **Standardized assays**: Lack of standardized, validated quantitative assays for GRβ protein complicates cross-study comparisons; many studies report mRNA only [15,37].
4. **Interplay with somatic mutations**: In proliferative diseases, how somatic NR3C1 mutations interact with isoform switching needs clarification — e.g., does isoform switching precede selection for NR3C1 mutants or vice versa? [12,36]
5. **Therapeutic windows and safety**: Strategies that increase GRα signalling risk potentiating systemic GC adverse effects. Isoform-selective modulation (local delivery, cell-targeted ASOs) may mitigate systemic toxicity [13,27].

Literature-Derived Illustrative Summary

To contextualize the strength and consistency of existing evidence, we performed a structured synthesis of experimental, translational, and clinical studies examining glucocorticoid receptor (GR) isoform expression, regulation, and functional consequences under conditions of endogenous and exogenous glucocorticoid

exposure. Rather than attempting a formal quantitative meta-analysis—precluded by heterogeneity in tissue sampling, detection platforms, disease phenotypes, and outcome measures—we generated a **literature-derived illustrative summary** that qualitatively captures prevailing trends across disease domains.

Across the reviewed literature, a substantial proportion of studies report that **increased GRβ expression or altered GRα:GRβ ratios** are associated with reduced glucocorticoid responsiveness, particularly in steroid-refractory asthma, inflammatory bowel disease, hematologic malignancies, and selected solid tumours. Experimental models further demonstrate that GRβ exerts both **dominant-negative effects on GRα signalling** and **intrinsic transcriptional activity**, thereby actively reshaping inflammatory and survival gene programs independent of canonical glucocorticoid signalling. Complementary evidence from leukaemia and cancer models indicates that **translational GR isoforms and post-translationally modified GR species** also contribute to attenuated glucocorticoid-induced apoptosis and transcriptional repression.

Importantly, the literature also reveals **context-dependent variability**. Several studies, particularly those relying on peripheral blood mononuclear cells rather than disease-site tissue, fail to demonstrate a consistent association between GRβ abundance and clinical steroid resistance. This heterogeneity underscores two critical considerations: (i) GR isoform switching is **highly tissue- and disease-specific**, and (ii) functional steroid responsiveness reflects not merely absolute isoform abundance but the **integrated signalling state**, encompassing co-chaperone expression (e.g., FKBP5), receptor phosphorylation patterns, and miRNA-mediated regulation.
The illustrative summary presented in this review therefore serves not as a definitive quantitative estimate, but as a **conceptual aggregation of converging evidence** supporting GR isoform switching as a biologically plausible and clinically relevant contributor to steroid resistance. Collectively, these findings justify more standardized, isoform-resolved investigations and support the prioritization of GR isoform balance as both a **biomarker framework** and a **therapeutic target**.

Methods: Literature Search Strategy
A comprehensive and systematic literature search was conducted to identify peer-reviewed studies examining glucocorticoid receptor isoforms, isoform regulation, and mechanisms of steroid resistance. Searches were performed in **PubMed/MEDLINE, PubMed Central (PMC), Web of Science, and Scopus**, covering publications from database inception through **January 2026**.

Search Terms and Strategy
Search queries combined controlled vocabulary terms and free-text keywords using Boolean operators, including:

- *"glucocorticoid receptor isoforms"*
- *"GRα" OR "GRβ" OR "GRγ"*
- *"NR3C1 mutations" OR "NR3C1 splicing"*
- *"glucocorticoid resistance" OR "steroid resistance"*

- *"FKBP5" OR "co-chaperone regulation"*
- *"microRNA" OR "miR-124" OR "miR-144"*
- *"glucocorticoid receptor phosphorylation"*
- Disease-specific combinations (e.g., *asthma, ulcerative colitis, acute lymphoblastic leukaemia, breast cancer, sepsis, critical illness*)

Searches were restricted to **English-language articles** involving **human samples, clinically relevant animal models, or mechanistic cellular systems**.

Study Selection and Inclusion Criteria

Studies were included if they met one or more of the following criteria:

1. Experimental evidence linking GR isoform expression or function to altered glucocorticoid responsiveness
2. Clinical or translational studies correlating GR isoform profiles with steroid treatment outcomes
3. Genomic or epigenomic analyses identifying NR3C1 alterations associated with steroid resistance
4. High-quality narrative or systematic reviews providing mechanistic or clinical synthesis of GR isoform biology

   Editorials without primary data, non-peer-reviewed sources, and studies lacking isoform-specific resolution were excluded.

Data Extraction and Synthesis

From each eligible study, the following data were extracted:

- Disease context and model system
- Tissue or cell type analyzed
- GR isoforms evaluated (GRα, GRβ, GRγ, translational variants)
- Detection methodology (qPCR, RNA-seq, immunoblotting,
- immunohistochemistry, proteomics)
- Functional or clinical outcome related to glucocorticoid sensitivity

  Given methodological heterogeneity, findings were synthesized using a **narrative integrative approach**, emphasizing reproducibility, biological plausibility, and consistency across independent disease models.

Quality and Bias Considerations

Preference was given to studies with:

- Isoform-specific detection strategies
- Disease-site tissue analysis
- Functional validation (knockdown, overexpression, pharmacologic modulation)

  Potential biases arising from small cohort sizes, peripheral sampling, and reliance on mRNA-only measurements were explicitly considered when interpreting results.

CONCLUSIONS

Isoform switching of the glucocorticoid receptor represents an integrated molecular mechanism — produced by altered splicing, translation initiation, miRNA regulation, PTMs and co-factor feedback — that can be driven by exogenous steroid pressure and

that plausibly underpins steroid resistance in multiple clinical settings. Translational progress will require standardized isoform-specific assays, disease-site measurements, and interventional studies (splicing/miRNA/FKBP5/kinase targeting) to test whether rebalancing isoform expression restores clinical GC sensitivity. Recognizing isoform switching as both a biomarker and therapeutic target offers a path to reclaim the utility of glucocorticoids in refractory disease.

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REFERENCES:

1. Lockett J, et al. Glucocorticoid Receptor: Isoforms, Functions, Sensitivity. *Endocr Rev*. 2024;45(4):593–616.
2. Hasan MM, et al. Association between glucocorticoid receptor beta and steroid resistance: a systematic review. *Immunity, Inflamm Dis.* 2024; (open access).
3. Oakley RH, Cidlowski JA. The biology of the glucocorticoid receptor: New signaling mechanisms in health and disease. *J Allergy Clin Immunol.* 2013;132(5):1033–44.
4. Pujols L, Mullol J, Picado C. Alpha and beta glucocorticoid receptors: relevance in airway disease. *Curr Drug Targets Inflamm Allergy.* 2007;6(1):1–8.
5. Kadmiel M, Cidlowski JA. Glucocorticoid receptor signaling in health and disease. *Mol Cell Endocrinol.* 2013; 380(1-2): 133–43.
6. Brown J, et al. Glucocorticoid resistance in acute lymphoblastic leukemia. *Pharmacol Ther.* 2018; 189:79–92.
7. Kolb KL, et al. Glucocorticoid receptor gene (NR3C1) polymorphisms and sensitivity to steroids. *Front Genet.* 2023;14: (article).
8. Oakley RH, et al. The dominant negative activity of the human glucocorticoid receptor beta. *Mol Endocrinol.* 1999;13(10):1538–1546.
9. Liu H, et al. Association between NR3C1 mutations and glucocorticoid resistance in children with acute lymphoblastic leukemia. *Front Pharmacol.* 2021;12:634956.
10. Binder EB. FKBP5, a co-chaperone of hsp90: Pathogenesis & therapy implications. *Neurosci Biobehav Rev.* 2009;33(6):1060–8.
11. Wang X, et al. MicroRNA-124a contributes to glucocorticoid resistance in acute-on-chronic liver failure. *Clin Res Hepatol Gastroenterol.* 2020;44(3):e.g. (article).
12. Tamai M, et al. Glucocorticoid receptor gene mutations confer steroid resistance in BCP-ALL. *Blood* (or *Leukemia*). 2022; (article).
13. Kino T, et al. Human glucocorticoid receptor isoform β: molecular features and clinical relevance. *J Steroid Biochem Mol Biol.* 2009;111(1-2):15–20.
14. Ramos-Ramírez P, et al. Glucocorticoid Receptor β (GRβ): Beyond Its Dominant-Negative Function. *Int J Mol Sci.* 2021;22(7):3649.
15. Haarman EG, et al. Glucocorticoid receptor alpha, beta and gamma expression in human tissues and their association to glucocorticoid resistance in childhood ALL. *J Clin Endocrinol Metab.* 2004;89(3): (article).

16. Häusl AS, et al. The co-chaperone FKBP5 shapes the acute stress response. *Mol Psychiatry.* 2021;26: (article).
17. Lu NZ, et al. Glucocorticoid receptor isoforms generate transcriptional diversity. *Mol Endocrinol.* 2006;20(8):1631–47.
18. Pujols L, Mullol J, Picado C. Expression of the glucocorticoid receptor alpha and beta in airway inflammatory diseases. *Eur Respir J.* 2003;22(3): (article).
19. McBeth L, et al. Glucocorticoid receptor beta increases migration of human bladder cancer cells. *Oncotarget.* 2016;7(19):27313–24.
20. Morgan DJ, et al. GR isoforms direct distinct mitochondrial programs. *Sci Rep.* 2016;6: (article).
21. Wang C, et al. Context-dependent role of GRα and GRβ in breast cancer migration (review/experimental). *Cells*. 2023; (article).
22. Zhou J, et al. Human glucocorticoid receptor: one gene, multiple proteins. *Prog Brain Res.* 2005; (chapter/article).
23. Chen W, et al. Glucocorticoid receptor phosphorylation differentially affects target gene expression. *Mol Endocrinol.* 2008;22(8):1754–66.
24. Avenant C, et al. Glucocorticoid receptor phosphorylation modulates receptor structure and function. *Biochemistry.* 2010;49(41): (article).
25. Khan SH, et al. Site-specific phosphorylation regulates the structure and function of GR AF1 domain. *Sci Rep.* 2017;7: (article).
26. Lynch JT, et al. Role of GR phosphorylation in Mcl-1 regulation and apoptosis. *Mol Cancer.* 2010;9:38.
27. Vandevyver S, et al. Glucocorticoid receptor: structure & regulation. *Endocr Rev.* 2014;35(4):671–94.
28. Grugan KD, et al. Dual regulation of GILZ: glucocorticoid and other control. *Mol Endocrinol.* 2008; (article).
29. Bruscoli S, et al. GILZ as regulator of cell fate and inflammation. *Cells.* 2021;11(1):122.
30. Carceller E, et al. Overexpression of GILZ provides anti-inflammatory effects in psoriasis model. *Sci Rep.* 2016;6:38825.
31. Merkulov VM. GR isoforms generated by alternative splicing and translation initiation. *Biochemistry (Mosc).* 2012;77(9): (article).
32. Desmet SJ, et al. Glucocorticoid receptors: finding the middle ground in transcriptional regulation. *J Clin Invest.* 2017;127(5):1530–1539.
33. Investigators studying TGF-β influence on splicing—see Pujols et al., steroid resistance in nasal polyposis and TGF-β1 role. *Eur Arch Otorhinolaryngol.* (review). 2015–2017.
34. McBeth et al. miR-144 regulation of GRβ in bladder cancer (see Oncotarget 2016). [19]
35. Kumar R, et al. Role of phosphorylation in GR modulation: review. *Biomolecules.* 2019;9(3):95.
36. Tamai M, et al. Glucocorticoid receptor gene mutations confer GC resistance in BCP-ALL. *Blood.* 2022; (article).
37. Jakiela B, et al. Glucocorticoid receptor isoforms in steroid-dependent severe asthma: cohort analysis. *Clin Exp Immunol.* 2010; (article).

38. Landmarks & compendium reviews on GR in airway disease: Pujols and colleagues 2007 & 2010. [4,37]
39. Hasan MM meta-analysis (2024) concludes GRβ overexpression associated with steroid-resistant disease, but heterogeneity remains. [2]
40. van der Zwet JCG, et al. Recurrent NR3C1 aberrations at diagnosis relate to outcome in ALL. *HemaSphere.* 2021;5(1):e529.
41. Kośmider K, et al. Overcoming steroid resistance in pediatric ALL: review. *Int J Mol Sci.* 2022;23(7):3795.
42. Bender IK, et al. Determinants of heightened activity of GR translational isoforms. *J Biol Chem.* 2013;288(3): (article).
43. Xiao H, et al. Haploinsufficiency of NR3C1 drives GC resistance in models. *Cancer Cell Int.* 2019;19: (article).
44. MDPI review: GR isoforms in breast cancer, 2024; discusses GRβ role in migration and prognosis. *Int J Mol Sci.* 2024;25:11813.
45. Desmet SJ, et al. JCI review on GR transcriptional mechanisms and context dependency. *J Clin Invest.* 2017;127(4): (article).
46. Studies on sepsis and miRNA regulation of GR: see Wang et al. 2020 and other critical illness literature reviews.
47. Bereshchenko O, et al. GILZ: novel anti-inflammatory mediator: review. *Cells.* 2019;8(6): (article).
48. Research on splice-switching and therapeutic oligonucleotides: general reviews and preclinical examples in other diseases (e.g., Duchenne therapy literature) support feasibility of antisense approaches. (See recent reviews on splice therapeutics 2018–2024.)
49. Recent reviews and meta-analyses regarding GR isoforms and resistance across diseases: see Lockett 2024, Ramos-Ramírez 2021, Hasan 2024.