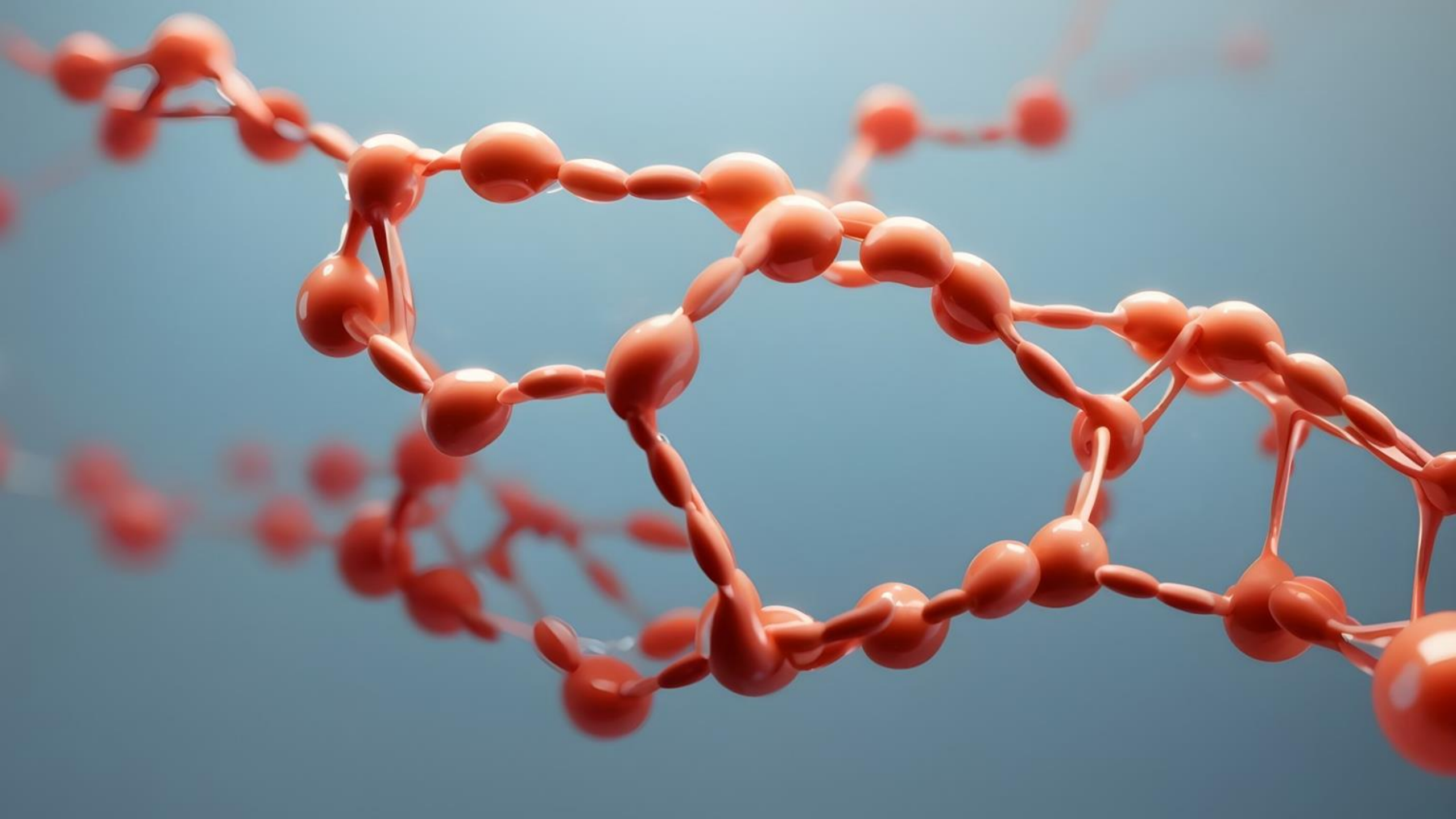
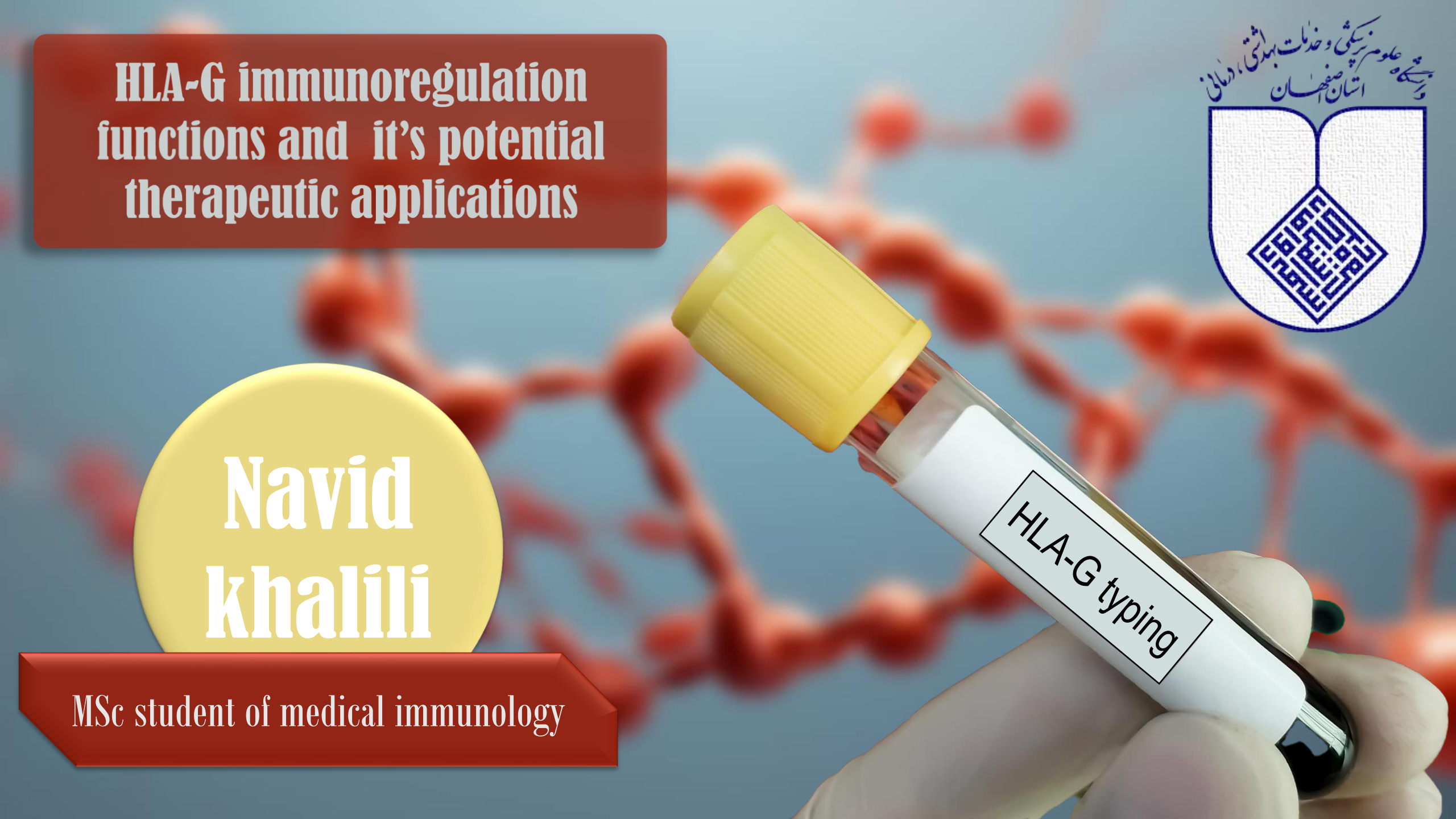


# HLA-G immunoregulation functions and it's potential therapeutic applications

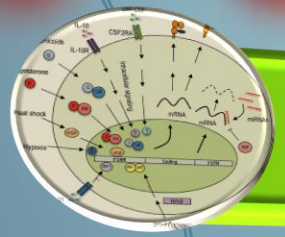

Navid khalili

MSc student of medical immunology

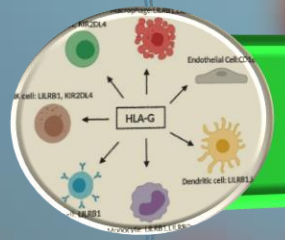



# OUTLINES

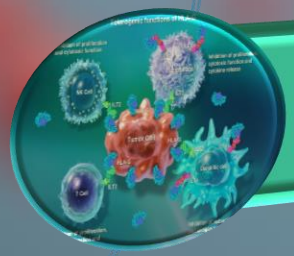
Introduction



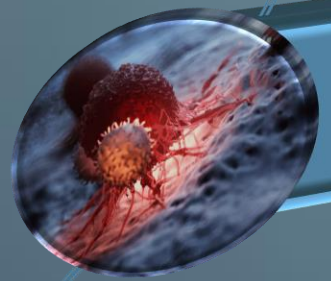
Polymorphisms and association with diseases




HLA-G in transplantation, autoimmunity, viral infections



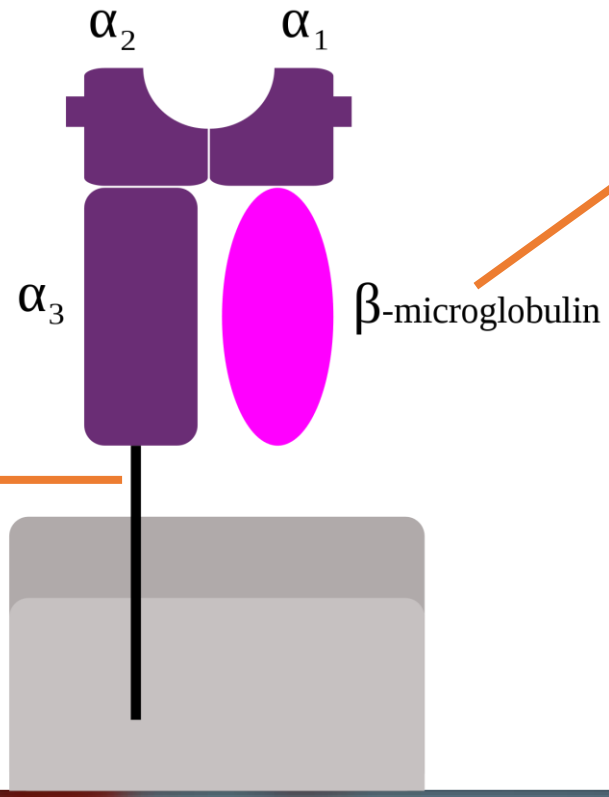
HLA-G as a immune checkpoint in cancers



Therapeutic applications

# Structure

- The heavy chain approximately weighs 45 kDa
- Locus position of heavy chain: 6p21.3




- Its weight is about 12KDa
- It is located on chromosome 15

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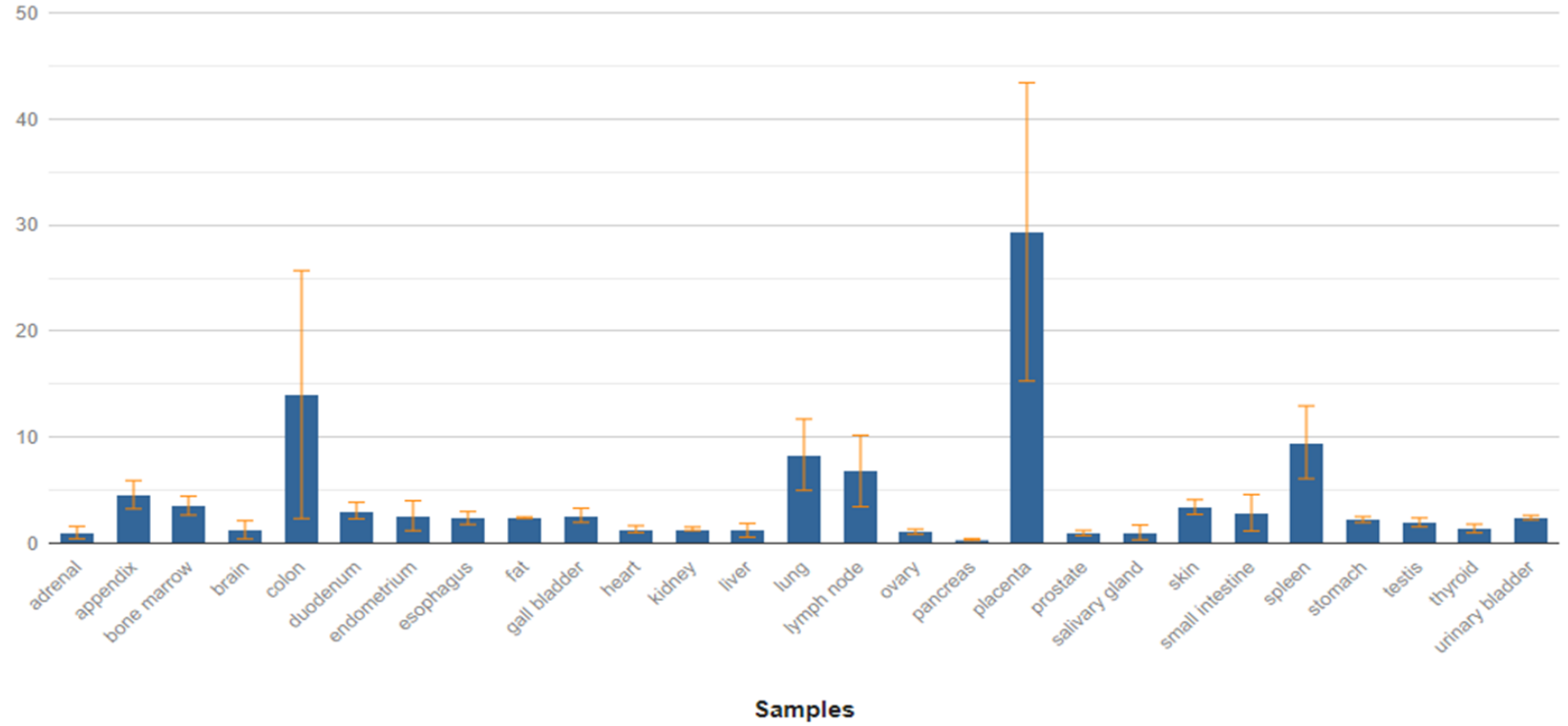
# Tissue distribution




NCBI

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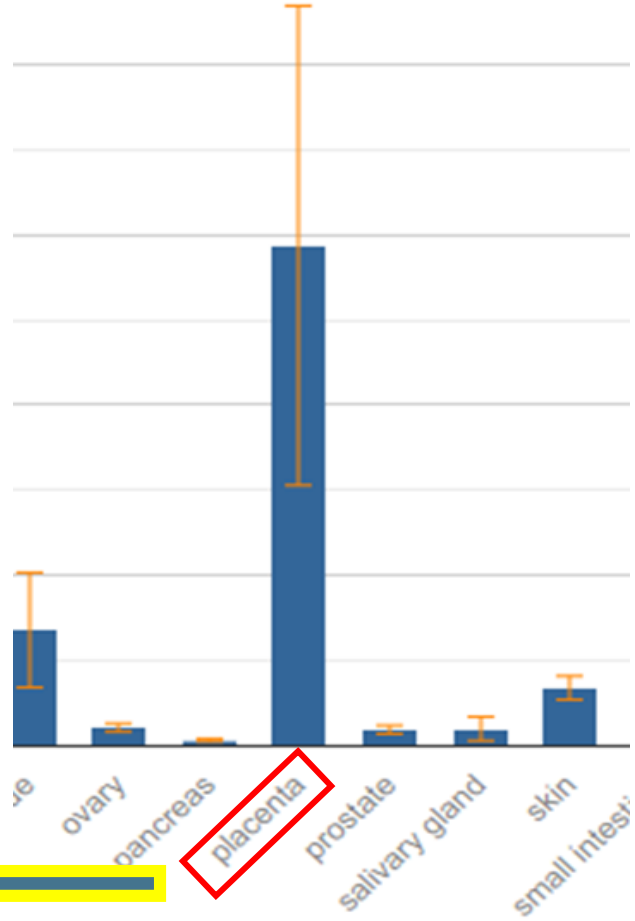
DOI: 10.3390/ijms21228678

# Tissue distribution

- HLA-G is mainly expressed on the extravillous cytotrophoblasts in the placenta, where it mediates maternal–fetal immune tolerance during pregnancy.

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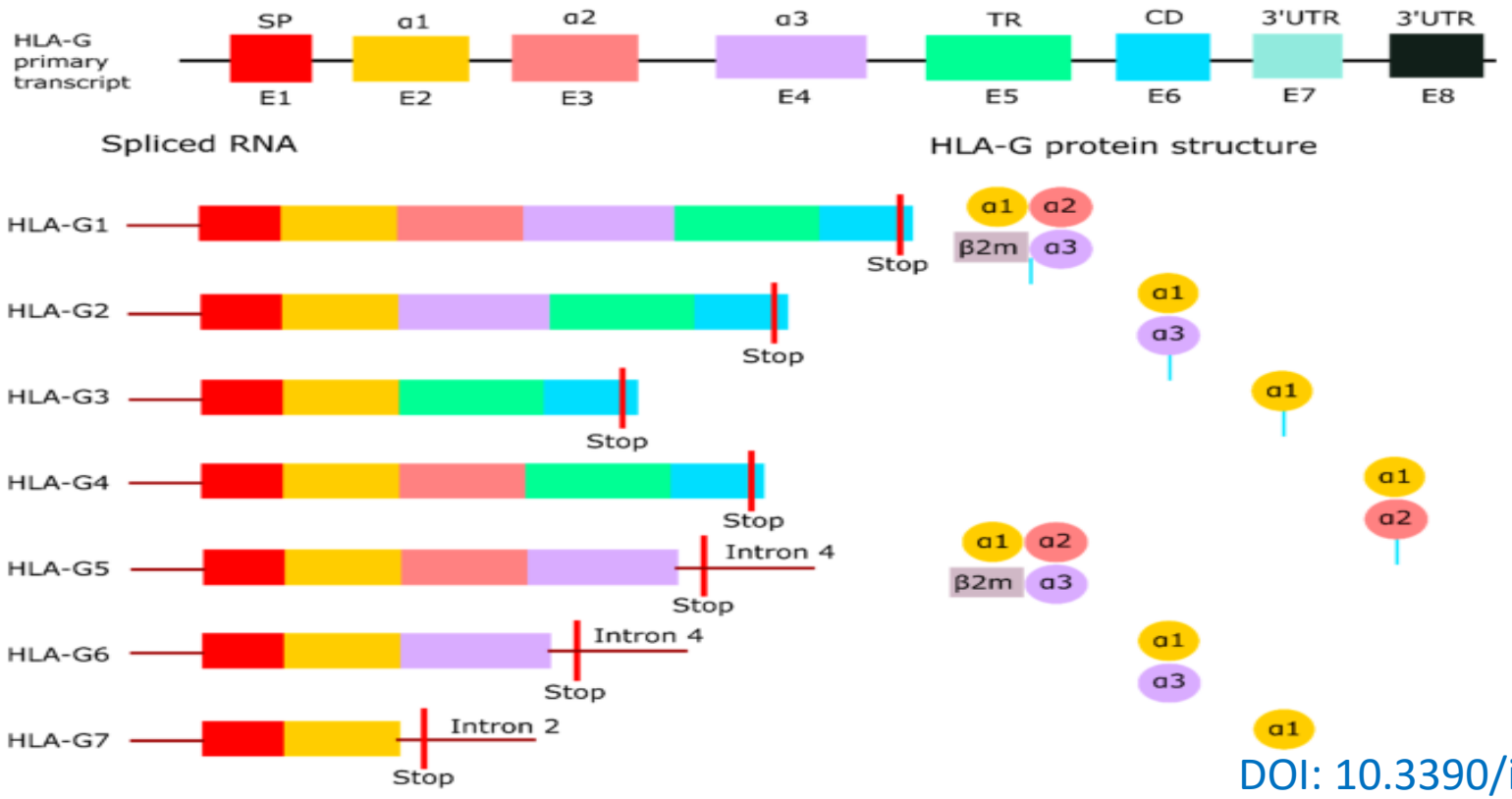
# Isoforms




DOI: 10.3390/ijms21228678

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# Peptide presentation

- Elution of HLA-G peptides revealed a heterogeneous and complex mixture of peptides, which was less diverse compared to peptides derived from classical HLA class I molecules.

- The majority of the peptides have a length of nine residues and are derived from intracellular proteins like nuclear proteins, cytosolic proteins, ribosomal proteins, cytokine receptors, histones.

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# Peptide presentation

Since HLA-G only presents a restricted number of peptides, it is questioned how peptide presentation contributes to the biological function of HLA-G.

It is suggested that the primary function of HLA-G is not antigen presentation. the peptides loaded onto HLA-G stabilize and prolong the expression of HLA-G, thereby enhancing its inhibitory capacities.

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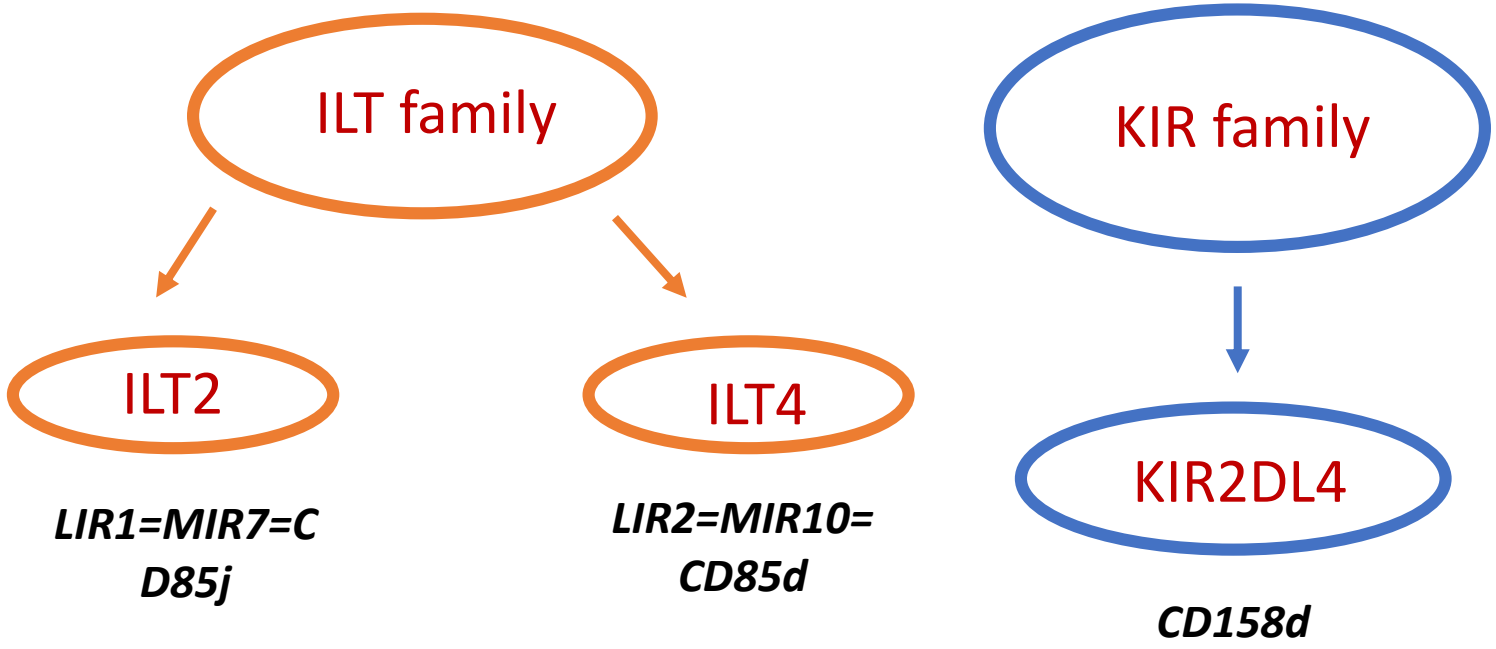
# HLA-G Receptors

- HLA-G interacts with various receptors that originate from different receptor families.

Two of the most important receptors are:

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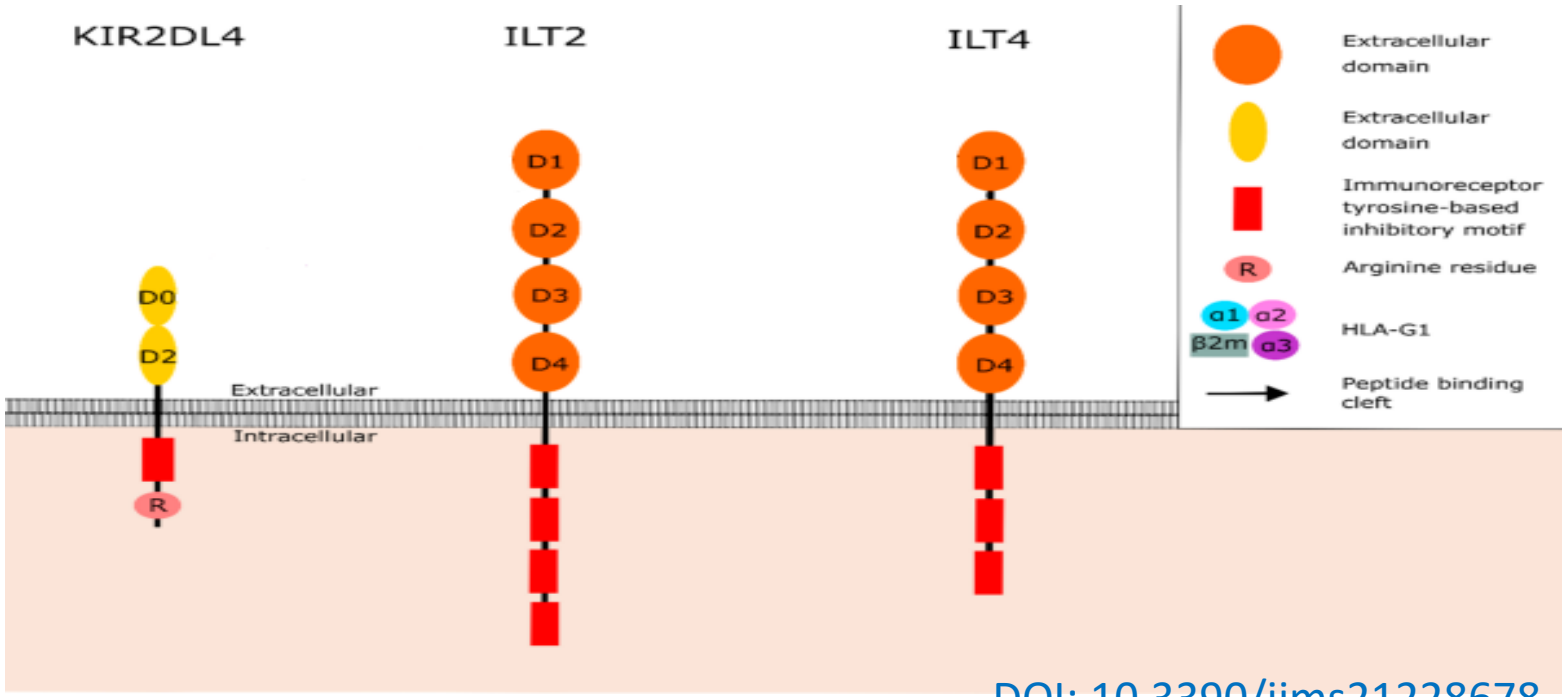
# HLA-G Receptors




DOI: 10.3390/ijms21228678

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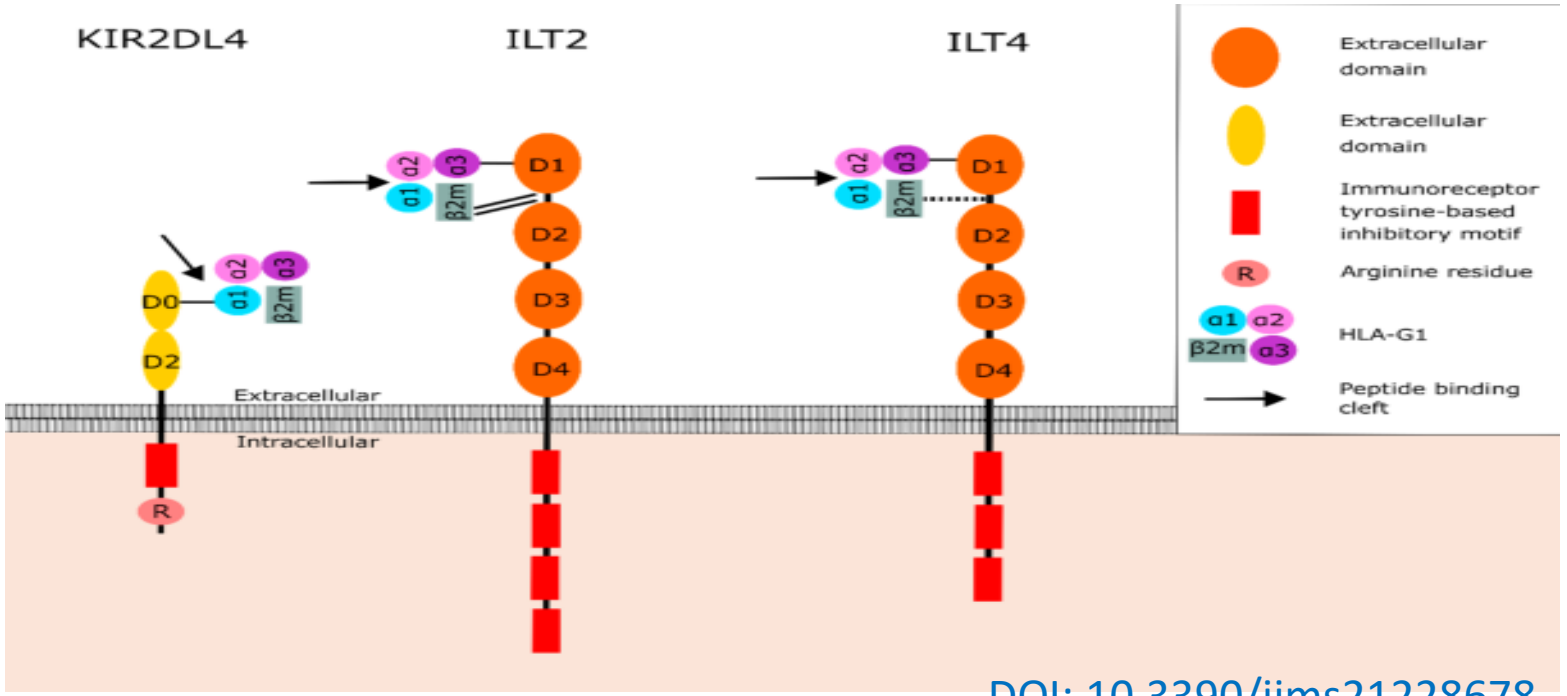
# HLA-G/receptor interaction




DOI: 10.3390/ijms21228678

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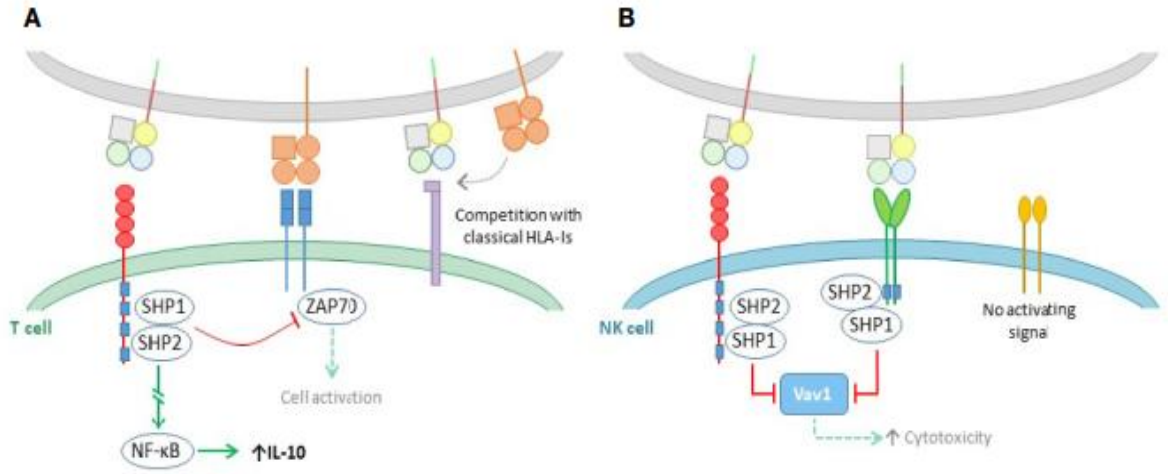
# Binding characteristics of HLA-G receptors and their function:




- Inhibition of cytotoxicity
- Inhibition of proliferation
- Inhibition of chemotaxis
- Induction of Tregs and Th2-type cytokine

- Inhibition of cytotoxicity
- Inhibition of proliferation
- Up-regulation of inhibitory receptors
- Inhibition of chemotaxis
- Reduced IFN-γ production

frontiers in Immunology

DOI: 10.3389/fimmu.2022.796054

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# HLA-G gene polymorphisms

So far, more than 88 different HLA-G alleles have been discovered.

Population studies have found nine polymorphic sites in the 3'UTR region of the HLA-G gene. Among them, the 14bp INS/DEL (5'-ATTTGTTCATGCCT-3') (rs371194629), +3142C/G (rs1063320) and +3187A/G (rs9380142) polymorphisms are implicated in HLAG expression.

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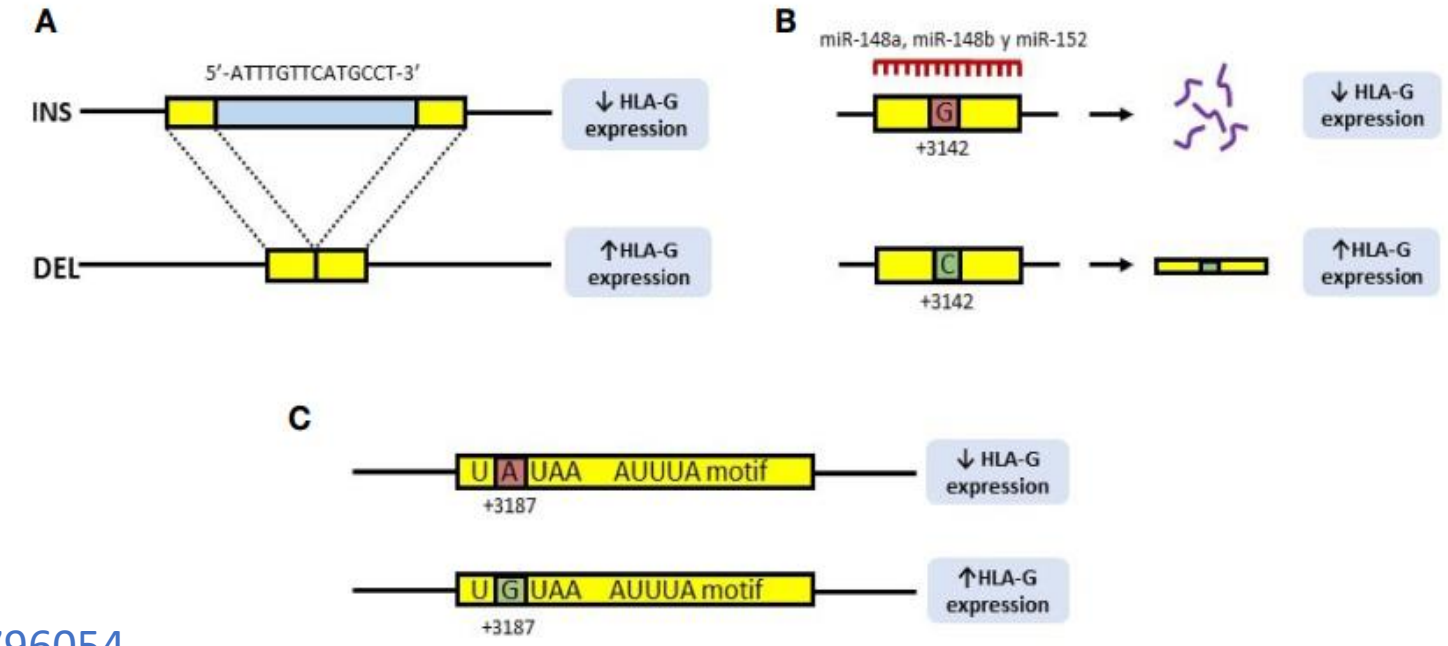
# HLA-G gene polymorphisms




frontiers in Immunology

DOI: 10.3389/fimmu.2022.796054

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# HLA-G gene polymorphisms and breast cancer

**Association between HLA-G 3'UTR 14-bp ins/del polymorphism and susceptibility to breast cancer**

Ebrahim Eskandari-Nasab [1], Mohammad Hashemi, Seyed-Shahaboddin Hasani, Mohsen Omrani, Mohsen Taheri, Mohammad-Ali Mashhadi

Affiliations + expand

PMID: 24240586 DOI: 10.3233/CBM-130364

- Eskandari-Nasab et al, Found that the HLA-G 14bp DEL/DEL genotype was higher in breast cancer patients than in the control group (33.9% vs 24.1%, respectively, p=0.006), suggesting that the 14bp INS/DEL polymorphism could be a genetic risk factor mediating susceptibility to breast carcinoma.

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# HLA-G and systemic lupus erythematosus

**Association of the *HLA-G* gene +3142C>G polymorphism with systemic lupus erythematosus**

C. R. Consiglio, T. D. Veit, O. A. Monticielo, T. Mucenic, R. M. Xavier, J. C. T. Brenol, J. A. B. Chies

First published: 14 March 2011 | https://doi.org/10.1111/j.1399-0039.2011.01635.x | Citations: 54

- Patients with SLE have a significant increase in the +3142G allele and the +3142G/G genotype of the +3142C>G polymorphism, associated with a lower expression of HLA-G due to increased degradation of the primary transcript, as well as by suppression of its translation.

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# HLA-G and psoriasis


DERMATOLOGIC THERAPY

Therapeutic Hotline

**HLA-G 14-bp polymorphism: a possible marker of systemic treatment response in psoriasis vulgaris? Preliminary results of a retrospective study**

Alessandro Borghi, Roberta Rizzo, Monica Corazza, Alberto Maria Bertoldi, Daria Bortolotti, Giulia Sturabotti, Annarosa Virgili, Dario Di Luca

First published: 09 June 2014 | https://doi.org/10.1111/dth.12140 | Citations: 12

- In the case of psoriasis, patients with the 14bp DEL allele and the DEL/DEL genotype of the 14bp INS/DEL polymorphism respond better to treatment with acitretin.

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# HLA-G and transplantation

**Human Leukocyte Antigen-G Expression After Heart Transplantation Is Associated With a Reduced Incidence of Rejection**

Nermine Lila, Catherine Amrein, Romain Guillemain, Patrick Chevalier, Christian Latremouille, Jean-Noël Fabiani, Jean Dausset, Edgardo D. Carosella and Alain Carpentier

**Originally published** 15 Apr 2002 |
https://doi.org/10.1161/01.CIR.0000015075.89984.46 |
Circulation. 2002;105:1949–1954

- The relationship between HLA-G and graft acceptance/rejection was first observed in heart transplantation.
- Studies reported the presence of HLA-G in biopsies of transplanted heart tissue, where HLA-G was especially prevalent in patients with no or low rejection scores.

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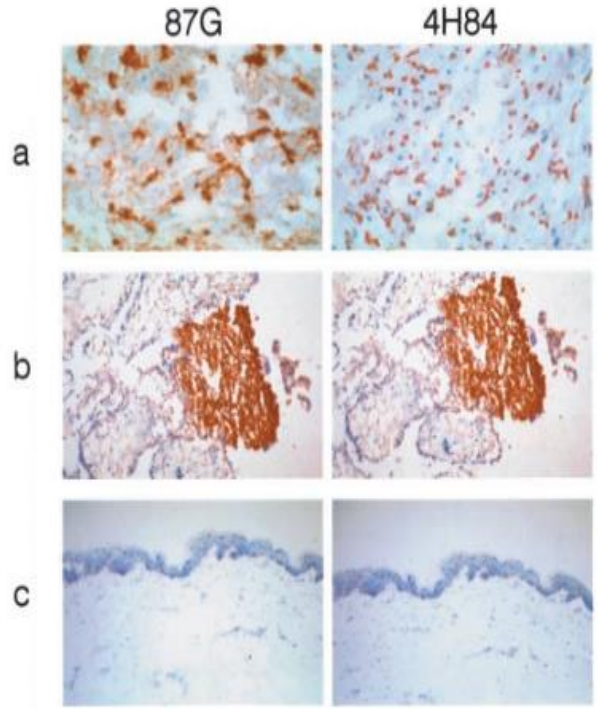
# HLA-G and transplantation

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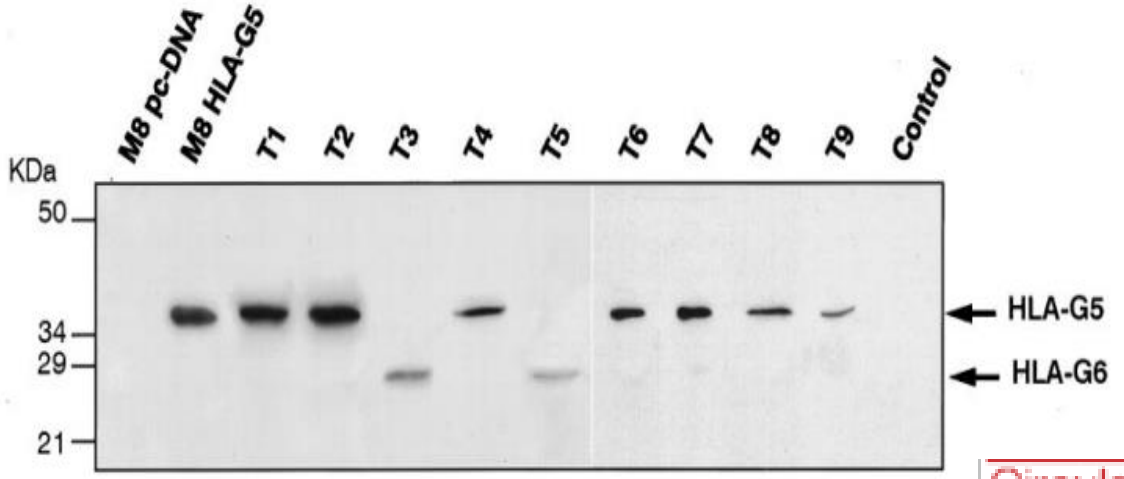


doi: 10.1161/01.cir.0000015075.89984.46
Circulation

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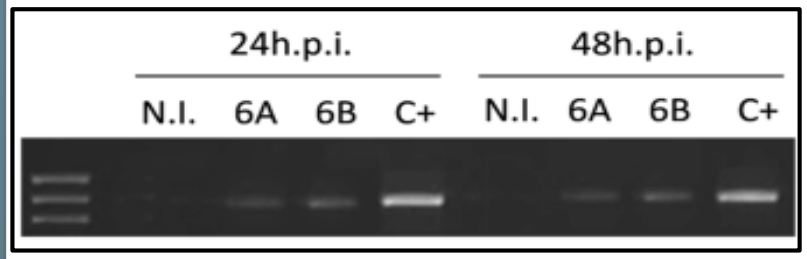
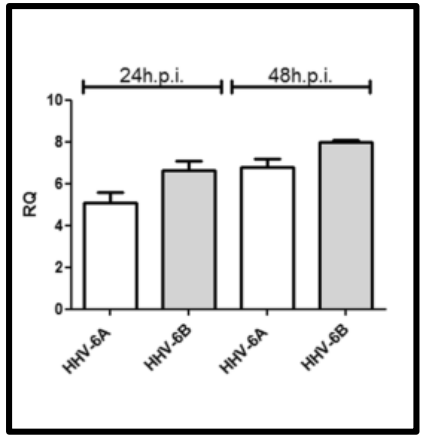
# HLA-G and human herpesvirus




SCIENTIFIC REPORTS

Article | Open access | Published: 06 December 2018

**Human Herpesvirus 6A and 6B inhibit *in vitro* angiogenesis by induction of Human Leukocyte Antigen G**

Roberta Rizzo, Maria D'Accolti, Daria Bortolotti, Francesca Caccuri, Arnaldo Caruso, Dario Di Luca & Elisabetta Caselli

- HHV-6A/B express the viral protein U94, which has key functions in the viral life cycle and elicits immune responses.

***U94*** → ***ATF3*** → ***Elevated expression of HLA-G***

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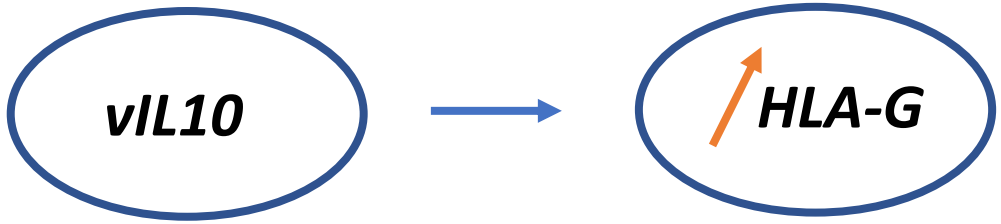
# HLA-G and EBV

- EBV has been reported to induce the HLA-G expression by yet undefined molecular mechanisms.




ELSEVIER

Human Immunology
Volume 68, Issue 6, June 2007, Pages 463-468

## HLA-G expression is induced in Epstein-Barr virus–transformed B-cell lines by culture conditions

**Table 2** Flow cytometry of Epstein-Barr virus-transformed B-cell lines cultured without replenishment with fresh medium and stained with MEM-G9/fluorescein isothiocyanate (% positive)

| Cell line number | 2 Days in culture | 4 Days in culture | 10 Days in culture |
|---|---|---|---|
| 6009 | 3.3 | 2.3 | 10.0 |
| 6013 | 1.9 | 1.5 | 5.8 |
| M | 4.1 | 5.2 | 18.7 |
| 6736 | 3.0 | 2.7 | 17.2 |
| 413 | 1.0 | 1.0 | 11.3 |
| 414 | 1.3 | 1.2 | 6.3 |
| OM | 4.0 | 4.1 | 16.8 |
| 6737 | 1.1 | 1.0 | 7.6 |
| 6138 | 0.5 | 0.8 | 3.2 |
| 6741 | 2.9 | 4.2 | 6.3 |
| 6656 | 2.7 | 2.1 | 7.8 |
| BA | 2.7 | 1.9 | 7.8 |
| 6393 | 2.7 | 2.2 | 11.1 |

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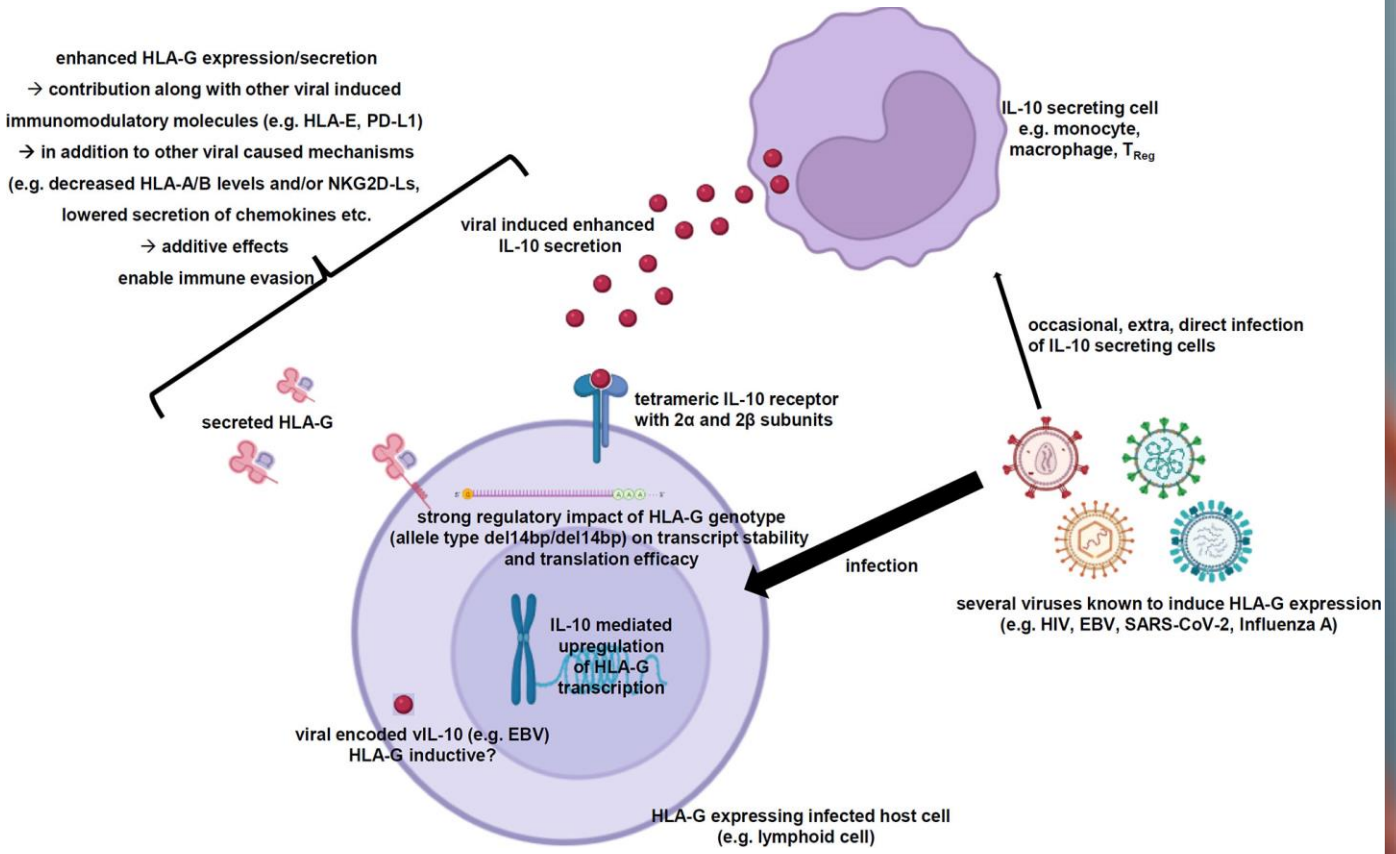
# HLA-G and EBV

- In many of studies a correlation of the HLA-G neo-expression with elevated IL-10 levels is reported. Indeed, IL-10 is a known inducer of the HLA-G expression.




doi.org/10.3389/fimmu.2022.826074

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# HLA-G as a new immune check point in cancer?

- HLA-G is mainly expressed on the extravillous cytotrophoblasts in the placenta, where it mediates maternal-fetal immune tolerance during pregnancy.
- While expression of HLA-G is restricted in healthy tissue, pathological conditions can induce HLA-G expression.
- De novo HLA-G expression has been observed, including in colorectal cancer, breast cancer, melanoma and ovarian cancer.

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# HLA-G as a new immune check point in cancer?

Due to its immune-inhibiting functions, Many studies have claimed HLA-G as a new immune checkpoint in cancer.

The first immune checkpoint inhibitors that were approved by FDA blocked the interaction between PD-1,CTLA-4 and their ligands.


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# Expression of HLA-G in tumor cells

Immune cells are inhibited when HLA-G binds to its receptors, tumor cells might profit from the expression of both HLA-G and its receptors.

Studies in patients with non-small lung carcinoma (NSCLC), gastric cancer, and CRC reported co-expression of HLA-G and its receptors ILT2 or ILT4 on tumor cells, and showed a correlation between co-expression and poor clinical outcome.

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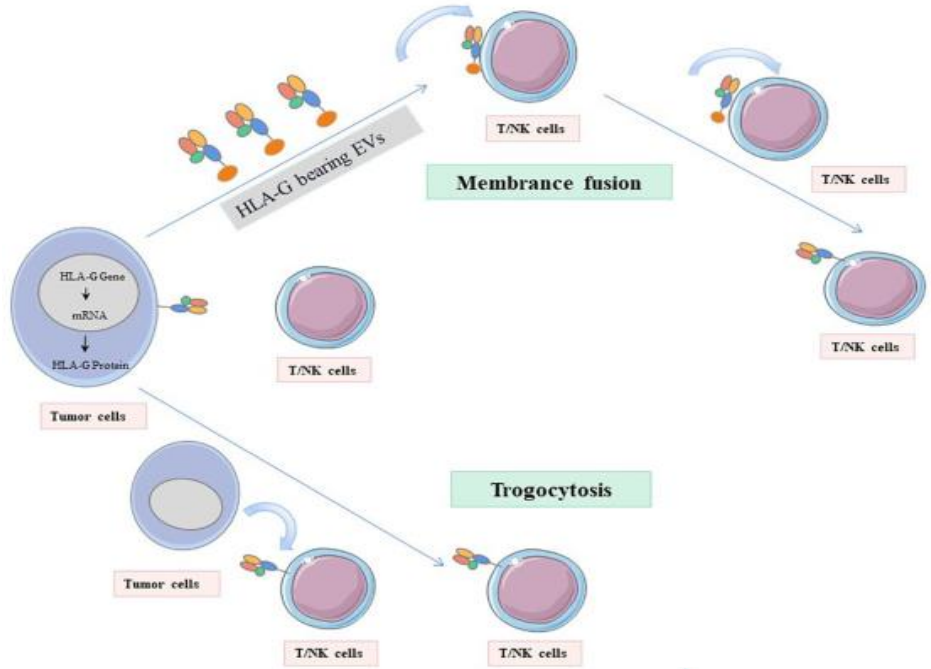
# HLA-G and tolerogenic function of immune cells




HLA-G-modified cells can immediately reverse immune effector functions to tolerogenic function.

doi: 10.3389/fimmu.2021.791535

frontiers in Immunology

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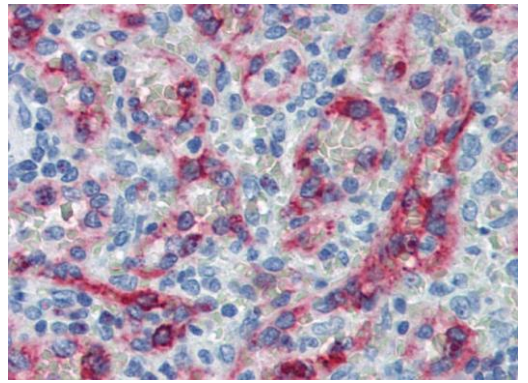
# sHLA-G as a tumor marker

- In the serum of healthy people, the content of HLAG is 20 ng/mL and significantly lower compared with cancer patients. sHLA-G is produced and secreted mainly by immune cells and tumors.

- For example, in acute leukemia, the level of sHLA-G in T cells and monocytes in the serum is detected by ELISA, which is averagely five times higher compared with healthy controls.



frontiers in Immunology doi: 10.3389/fimmu.2021.791535

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# Where to intervene for therapy?

## 1 Prevention of dimerization

Dimerization of HLA-G can be prevented by blocking the cysteine residue at position 42 in the α1 domain.

This can be achieved by targeting the α1 domain with antibodies that either directly block the cysteine residue, or sterically hinder dimerization.

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# Where to intervene for therapy?

## 2 Targeting receptors with mAbs

Another strategy is to target the HLA-G receptors with antibodies specifically binding to ILT2, ILT4 and/or KIR2DL4.

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# HLA-G as a target for immune checkpoint inhibition in cancer:

Basic tumor immunology
Original research

## Antagonistic anti-LILRB1 monoclonal antibody regulates antitumor functions of natural killer cells

Heyu Chen [1], Yuanzhi Chen [2, 3], Mi Deng [1], Samuel John [4], Xun Gui [2], Ankit Kansagra [5, 6], Weina Chen [7], Jaehyup Kim [7], Cheryl Lewis [6], Guojin Wu [1], Jingjing Xie [1], Lingbo Zhang [1, 8], Ryan Huang [1], Xiaoye Liu [1], Hisashi Arase [9], Yang Huang [3], Hai Yu [3], Wenxin Luo [3], Ningshao Xia [3], Ningyan Zhang [2], Zhiqiang An [2] and Cheng Cheng Zhang [1]

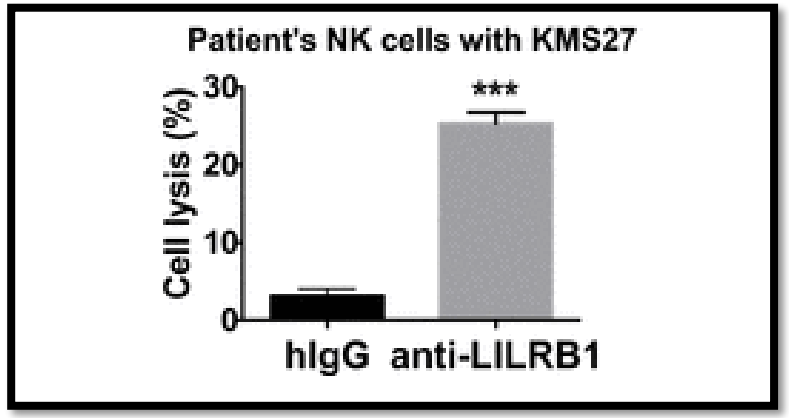
Correspondence to Dr Cheng Cheng Zhang; Alec.Zhang@UTSouthwestern.edu; Dr Ningyan Zhang; Ningyan.Zhang@uth.tmc.edu; Dr Zhiqiang An; Zhiqiang.An@uth.tmc.edu

# HLA-G as a target for immune checkpoint inhibition in cancer:

Basic tumor immunology
Original research

Antagonistic anti-LILRB1 monoclonal antibody regulates antitumor functions of natural killer cells

Heyu Chen [1], Yuanzhi Chen [2, 3], Mi Deng [1], Samuel John [4], Xun Gui [2], Ankit Kansagra [5, 6], Weina Chen [7], Jaehyup Kim [7], Cheryl Lewis [6], Guojin Wu [1], Jingjing Xie [1], Lingbo Zhang [1, 8], Ryan Huang [1], Xiaoye Liu [1], Hisashi Arase [9], Yang Huang [3], Hai Yu [3], Wenxin Luo [3], Ningshao Xia [3], Ningyan Zhang [2], Zhiqiang An [2] and Cheng Cheng Zhang [1]
Correspondence to Dr Cheng Cheng Zhang; Alec.Zhang@UTSouthwestern.edu; Dr Ningyan Zhang; Ningyan.Zhang@uth.tmc.edu; Dr Zhiqiang An; Zhiqiang.An@uth.tmc.edu




We also isolated NK cells from the peripheral blood of one patient with MM whose NK cells was about 80% LILRB1 positive, and used the patient's NK cells for cytotoxic assay. Anti-LILRB1 mAb increased cytotoxic activity of patient's NK cells against MM cell line KMS27.

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# Clinical trials

Int J Mol Sci. 2022 Mar; 23(6): 2925.
Published online 2022 Mar 8. doi: 10.3390/ijms23062925
PMCID: PMC8948858
PMID: 35328349

HLA-G and Other Immune Checkpoint Molecules as Targets for Novel Combined Immunotherapies

Fabio Morandi* and Irma Airoldi

Philippe Moreau, Academic Editor

## Combination therapy

- different antibodies against CTLA-4 and PD-1 have been developed for clinical purposes and used for immunotherapy in patients with glioblastoma.
- more than 50 clinical trials based on PD-1 blockade are currently active for glioblastoma patients.
- The expression of HLA-G and its role in cancer progression has been addressed in glioblastoma.

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# Clinical trials

- TTX-080-001 is a Phase 1, open label, dose escalation and dose expansion clinical study to determine the safety, tolerability, and recommended Phase 2 dose of TTX-080 monotherapy (HLA-G inhibitor) and in combination with either pembrolizumab (PD-1 inhibitor) or cetuximab (EGFR inhibitor) in patients with advanced refractory / resistant solid malignancies, including HNSCC, NSCLC, CRC, TNBC.


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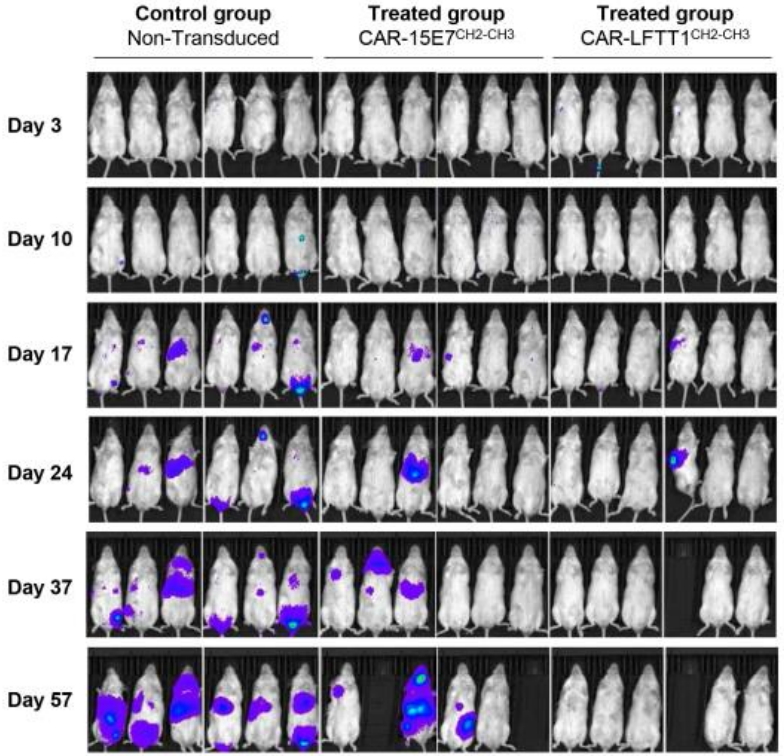
# CAR-T cell therapy against HLA-G




Journal for ImmunoTherapy of Cancer

Open access Original research

Journal for ImmunoTherapy of Cancer

## First immunotherapeutic CAR-T cells against the immune checkpoint protein HLA-G

François Anna,[1,2] Elodie Bole-Richard,[3,4,5] Joel LeMaoult,[6,7] Marie Escande,[1] Martin Lecomte,[1] Jean-Marie Certoux,[3,4,5] Philippe Souque,[2] Francine Garnache,[3,4,5] Olivier Adotevi ,[3,4,5] Pierre Langlade-Demoyen,[1] Maria Loustau,[1] Julien Caumartin [1]

- Mice received activated non-transduced T cells or CAR-T (CAR-15E7CH2-CH3 or CAR-LFTT1CH2-CH3) cells on day 3 and were monitored by bioluminescence imaging over time.

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# Where to intervene for therapy?

Considering the broad and location-specific functions of HLA-G receptors, it is desired to only inhibit these receptors in the tumor microenvironment (TME), where the receptors mediate immune evasion.

Defective expression and function of ILT2 is associated with the autoimmune disease systemic lupus erythematosus.

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# Where to intervene for therapy?

## 3 Prodrug-formulated antibodies

These antibodies have a masking peptide that binds to a peptide binding site of the target receptor. The masking peptide is cleaved by tumor-associated proteases in the TME and, as a result, the antibody is released to bind the target antigen.

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# Where to intervene for therapy?

## 3 Prodrug-formulated antibodies

This approach is dependent on the presence of tumor-associated proteases. It has been observed that HLA-G expression in ovarian cell line upregulates matrix metalloproteinase 15 (MMP-15) expression in these cells and a correlation between HLA-G and MMP-15 expression is also seen in ovarian cancer patients.

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# Where to intervene for therapy?

4

Intervention by micro interference RNAs(miRNAs)

A study on renal cell carcinoma showed strong post-transcriptional gene regulation of HLA-G by miRNA-152, miRNA-148A, miRNA-148B, and miRNA-133A.

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# Where to intervene for therapy?

4

## Intervention by micro interference RNAs(miRNAs)

Interestingly, the stable overexpression of miRNA-148A and miRNA-133A in target cells caused the downregulation of HLA-G protein expression, thereby enhancing the NK cell-mediated killing of these cells in vitro.

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# TGF-β and induction of HLA-G expression

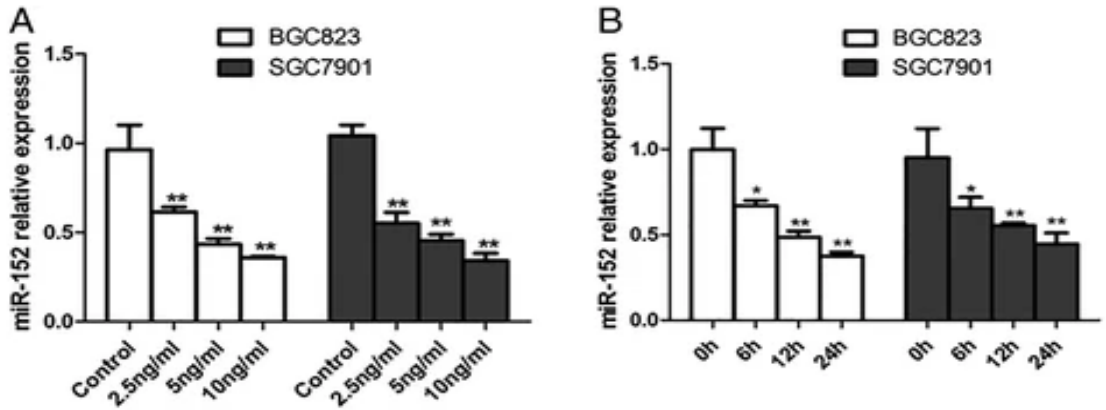
Research | Open access | Published: 02 December 2015

## TGF-ß induces HLA-G expression through inhibiting miR-152 in gastric cancer cells

Zhongzheng Guan, Bingtan Song, Fengjun Liu ✉, Dong Sun, Kexin Wang & Hui Qu

*Journal of Biomedical Science* **22**, Article number: 107 (2015) | Cite this article






TGF-β inhibited miR-152 levels in GC cell line. The expression of miR-152 was downregulated under TGF-β treatment in dosage (2.5, 5 or 10 ng/ml for 12 h; **a**) and time (5 ng/ml for 6, 10 or 24 h; **b**) dependent manner. $^{*}P < 0.05$; $^{**}P < 0.01$

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# Anti HLA-G antibodies

DOI: 10.3390/ijms21228678

**Table 2.** Overview of HLA-G-recognizing antibodies and their specificity.

| HLA-G mAbs | Specificity | Reference |
|---|---|---|
| 4H84 | An α1 epitope in HLA-G | McMaster et al., 1998 [87] |
| MEM-G/1 | Denatured free heavy chains of all HLA-G isoforms | Hurks et al., 2001 [88] |
| MEM-G/2 | Free heavy chains of all HLA-G isoforms | Polakova et al., 2003 [89] |
| MEM-G/4 | Free heavy chains of HLA-G1, -G2 and -G5 isoforms | Menier et al., 2003 [16] |
| MEM-G/9 | HLA-G1 and -G5 associated with β2M | Fournel et al., 2000 [90] |
| MEM-G/11 | HLA-G1 | Boyson et al., 2002 [91] |
| MEM-G/13 | HLA-G1 and -G5 | Menier et al., 2003 [16] |
| G233 | HLA-G1 and -G5 | Loke et al., 1997 [92] |
| 87G | HLA-G1 and -G5 | Ødum et al., 1991 [93] |
| 01G | HLA-G1 | Real et al., 1999 [94] |
| BFL.1 | HLA-G1 | Bensussan et al., 1995 [95] |
| 2A12 | HLA-G5 and -G6 | White et al., 2010 [96] |
| 5A6G7 | HLA-G5 and -G6 | Le Rond et al., 2004 [97] |
| 16G1 | HLA-G5 and -G6 | Blaschitz et al., 2000 [98] |

Abbreviations: β2-microglobulin (β2M), human leukocyte antigen G (HLA-G), monoclonal antibodies (mAbs).

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# Challenges and limitations with using anti-HLA-G antibodies

- The antibodies 4H84 and MEM-G/1 do recognize all HLA-G isoforms, but are known to cross-react with HLA class I molecules like HLA-A2.

- For future research, it is essential to develop antibodies that recognize all HLA-G isoforms, and to reduce the cross-reactivity of HLA-G-recognizing antibodies with other proteins. Moreover.

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THANK
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