The Dynamic Role of LGR5 in EGFR-Expressing Cancers

EGFR, epidermal growth factor receptor; LGR5, leucine-rich repeat-containing G-protein coupled receptor 5.

This Presentation Contains Three (3) Distinct Chapters

The Battle Against Epithelial Cancers

Burden and hallmarks

EGFR-targeted therapy

Treatment resistance

Pathogenic Plasticity

Plasticity (normal vs pathogenic)

Role of LGR5

LGR5 and clinical outcomes

LGR5, the Moving Target

LGR5 and cancer therapies

LGR5 protein recycling

Expression during metastasis

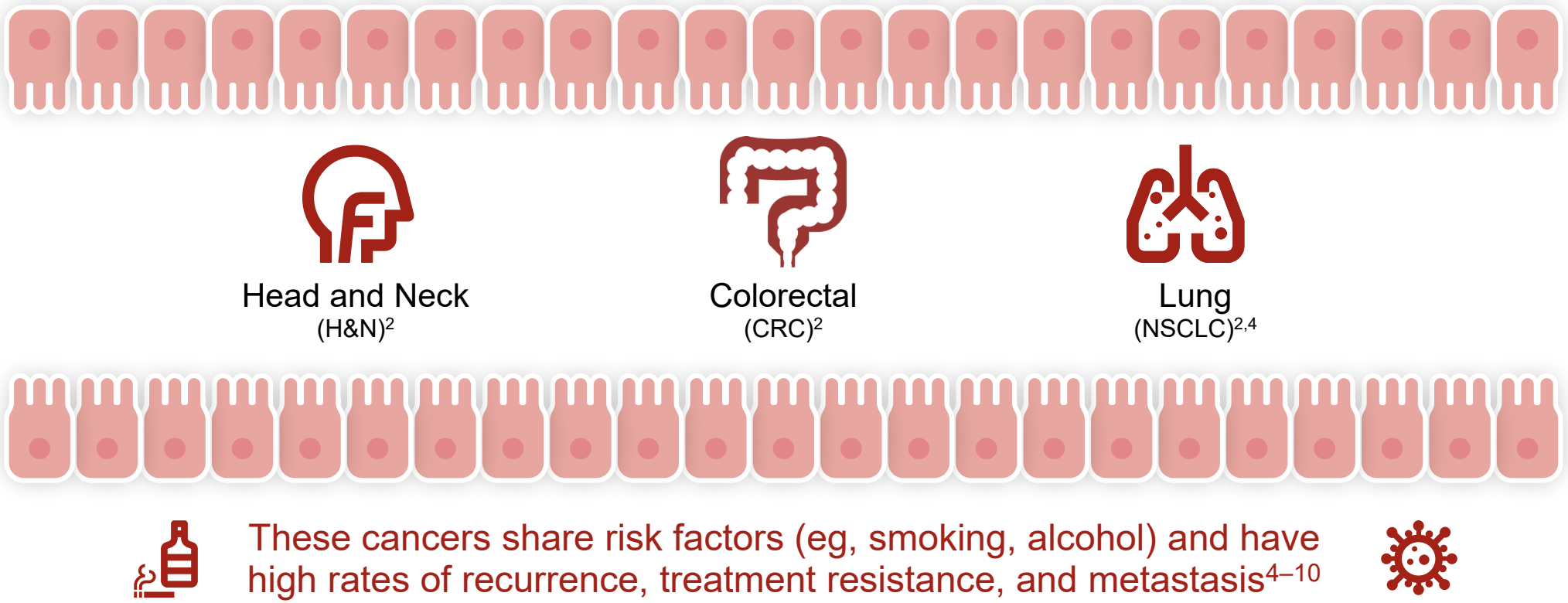
EGFR, epidermal growth factor receptor; LGR5, leucine-rich repeat-containing G-protein coupled receptor 5.

Chapter 1

The Battle Against Epithelial Cancers

Epithelial Cancers (Carcinomas) Arise From Cells That Line the Surfaces and Organs of the Body[1–3]

Examples of epithelial cancers



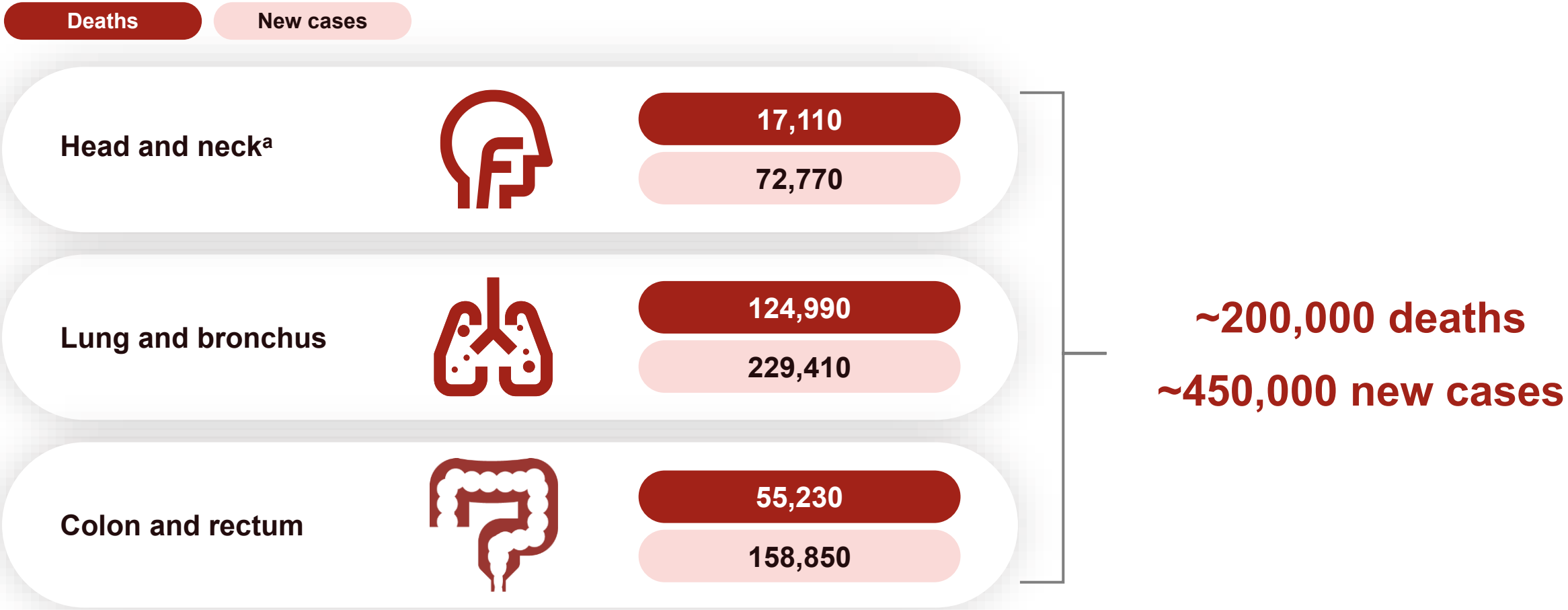
These cancers share risk factors (eg, smoking, alcohol) and have high rates of recurrence, treatment resistance, and metastasis[4–10]

NSCLC, non-small cell lung cancer.

1. National Cancer Institute. What is cancer? Accessed April 8, 2026. https://www.cancer.gov/about-cancer/understanding/what-is-cancer; 2. Cleveland Clinic. Carcinoma: types, treatment & what it is. Accessed April 8, 2026. https://my.clevelandclinic.org/health/ diseases/23180-carcinoma; 3. Features of Epithelial Tissues. In: Price T, et al. *Integrated Human Anatomy and Physiology*. Accessed April 8, 2026. https://uen.pressbooks.pub/anatomyphysiology/; 4. Tahayneh K, et al. *J Clin Med*. 2025;14(3):1025; 5. Hashibe M, et al. *Cancer Epidemiol Biomarkers Prev*. 2009;18(2):541-550; 6. Haring CT, et al. *Cancer*. 2023;129(18):2817-2827; 7. Barham WT, et al. *Cancers (Basel)*. 2025;17(1):144; 8. Amitay EL, et al. *Br J Cancer*. 2020;122(11):1604-1610; 9. Cervantes A, et al. *Ann Oncol*. 2023;34(1):10-32; 10. Oh JM, et al. *Front Immunol*. 2025;16:1571731.

H&N, CRC, and Lung Cancers Are Common in the US and Claim the Lives of Thousands of People Every Year

US Cancer Estimates (2026)



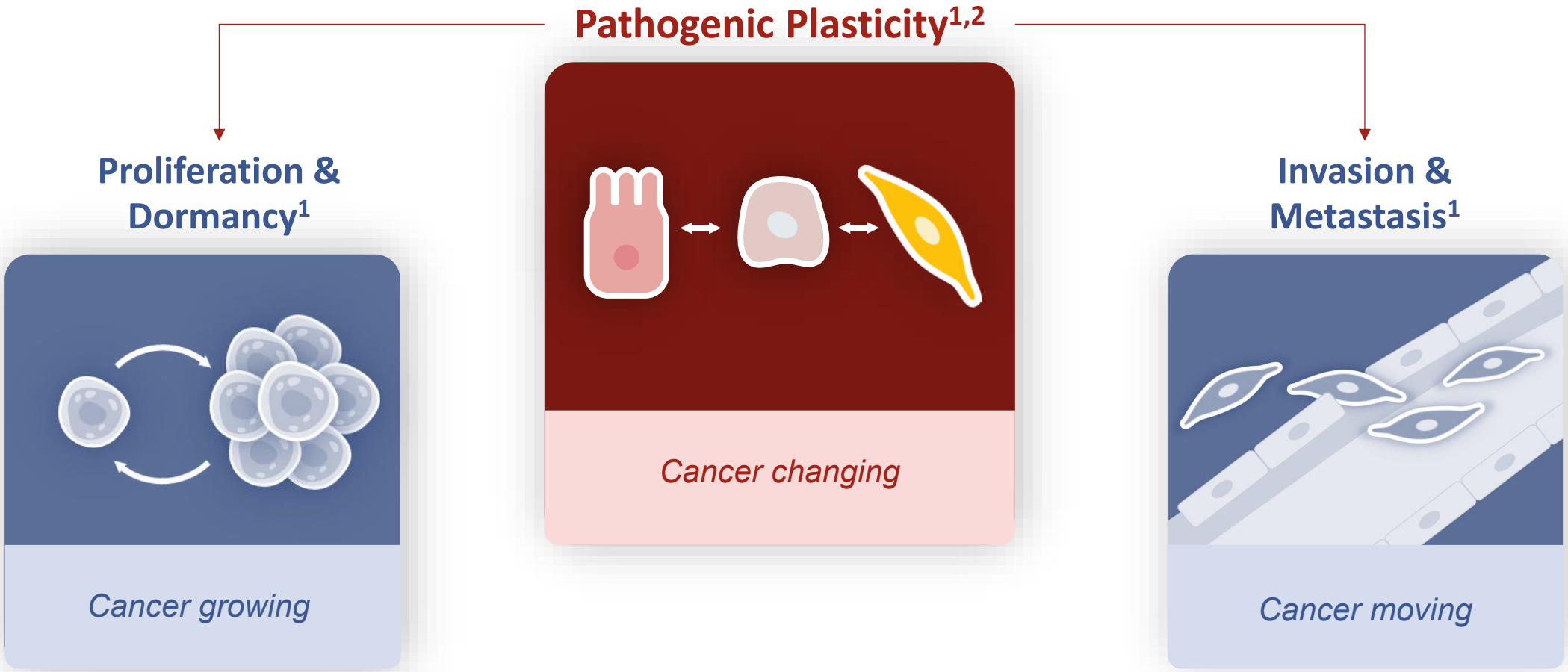
[a]Oral cavity, pharynx, larynx.

CRC, colorectal cancer; H&N, head and neck cancer; US, United States.

Siegel RL, et al. *CA Cancer J Clin*. 2026;76(1):e70043.

Pathogenic Plasticity Has Emerged as a Critical Cancer Hallmark[1,2]

Carcinomas Can Exploit Plasticity to Drive Disease Progression by Orchestrating Other Hallmarks[1]



1. Hanahan D. *Cancer Discov*. 2022;12(1):31-46; 2. Torborg SR, et al. *Trends Cancer*. 2022;8(9):735-746.

This Presentation Uses Terms That Are Interrelated

Clarifying Key Terms

Plasticity

Characteristic of stem-like cells that enables self-renewal and differentiation into other cell phenotypes[1,2]

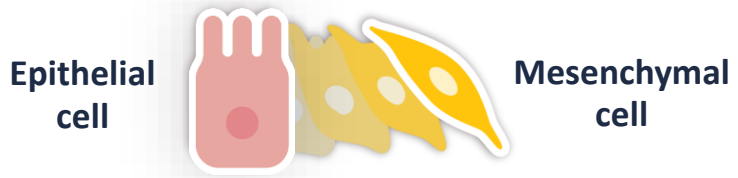
Pathogenic Plasticity

Cancer cells co-opting plasticity to initiate tumors, metastasize, and resist treatment[2]

Epithelial-Mesenchymal Transition (EMT)

An example of pathogenic plasticity that occurs in epithelial cancers[2–5]

- Epithelial cells lose their stationary characteristics (eg, cell-to-cell adhesion) and acquire mesenchymal traits that facilitate motility and invasion[5,6]
- Mesenchymal-epithelial-transition (MET) is the complementary process where epithelial characteristics are restored[6]



1. Du X, et al. *Front Cell Dev Biol*. 2026:14;1752590; 2. Torborg SR, et al. *Trends Cancer*. 2022;8(9):735-746; 3. Hanahan D. *Cancer Discov*. 2022;12(1):31-46; 4. Strauss R, et al. *Mol Ther*. 2012;20(5):887-897; 5. Mäkitie AA, et al. *Head Neck*. 2019;41(10):3712-3718; 6. Thompson EW, et al. *Nat Rev Clin Oncol.* 2025;22(10):711-733.

Plasticity Is a Mechanism of Resistance to EGFR-Targeted Therapy[1–3]

EGFR is overexpressed in 40%–97% of H&N, CRC, and NSCLC tumors[4–6]

Implicated in proliferation, metastasis, and survival[4,5]

EGFR-targeted therapies can block receptor signaling[4,5]

Epithelial cancers commonly develop resistance[4–6]

EMT is an established resistance mechanism[1–3a]

Cancer cells existing in a dynamic state with hybrid features[7]

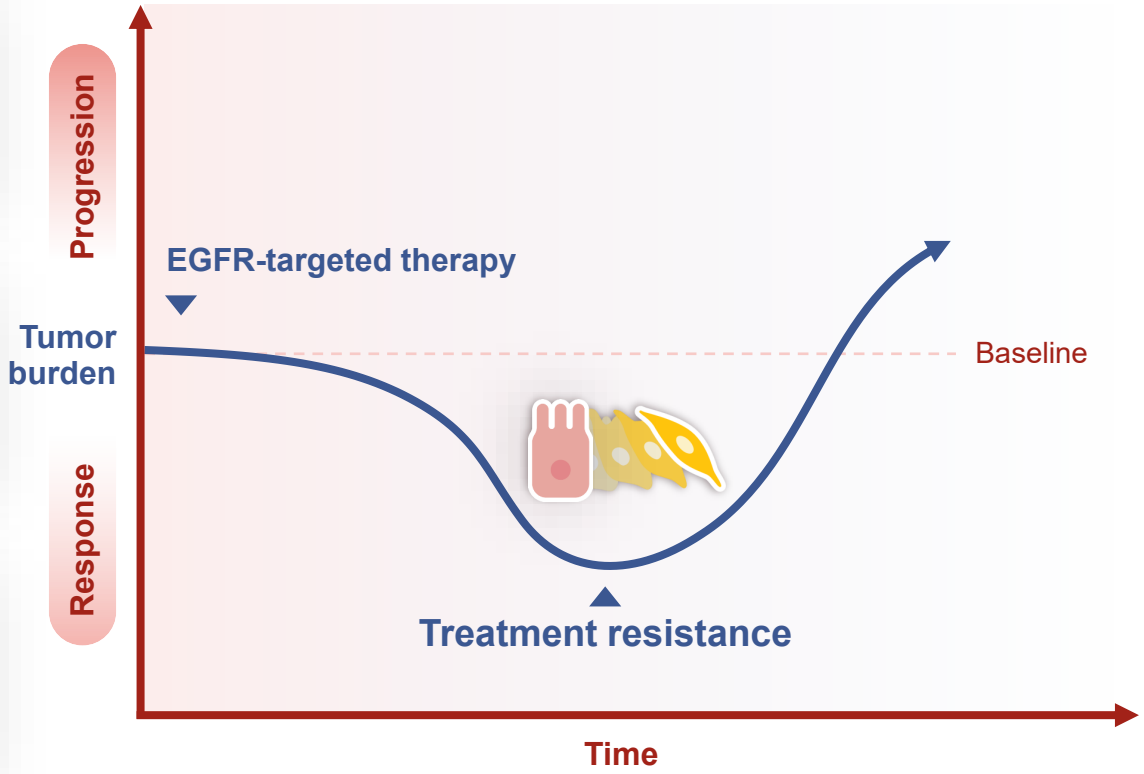


Figure is hypothetical and does not reflect data from a specific clinical study[8–10]

[a]Other resistance mechanisms include EGFR mutations (interference with treatment binding site) and downstream mutations (activation of signaling pathways that bypass EGFR).[1–3]

CRC, colorectal cancer; EGFR, epidermal growth factor receptor; EMT, epithelial-mesenchymal transition; H&N, head and neck cancer; NSCLC, non-small cell lung cancer.

1. Chhouri H, et al. *Cancers (Basel).* 2023;15(2):504; 2. Zhou J, et al. *J Exp Clin Cancer Res*. 2021;40(1):328; 3. Carosi F, et al. *Crit Rev Oncol Hematol*. 2026;221:105207; 4. Halder S, et al. *Expert Opin Ther Targets*. 2023;27(4-5):305-324; 5. London M, Gallo E. *Cell Biol Int*. 2020;44(6):1267-1282; 6. Xu MJ, et al. *Cancer Metastasis Rev.* 2017;36(3):463-473; 7. Thompson EW, et al. *Nat Rev Clin Oncol.* 2025;22(10):711-733; 8. Kobayashi K. *J Respir*. 2023;3(4):223-236; 9. Ciardiello D, et al. *Cancer Treat Rev*. 2024:124:102683; 10. Khattri A, et al. *Cancer Gene Ther*. 2024;31(10):1477-1485.

The Battle Against Epithelial Cancers

Key Takeaways

- **Epithelial cancers (eg, H&N, CRC, lung)** are common and have a **poor prognosis**, despite an established treatment target, EGFR[1,2]

- **Pathogenic plasticity has emerged as a critical hallmark of epithelial cancers** and can drive disease progression by orchestrating proliferation and metastasis[3,4]

- **EMT is an example** of pathogenic plasticity and a **resistance mechanism** to EGFR-targeted therapy[5–7]

CRC, colorectal cancer; EGFR, epidermal growth factor receptor; EMT, epithelial-mesenchymal transition; H&N, head and neck cancer.

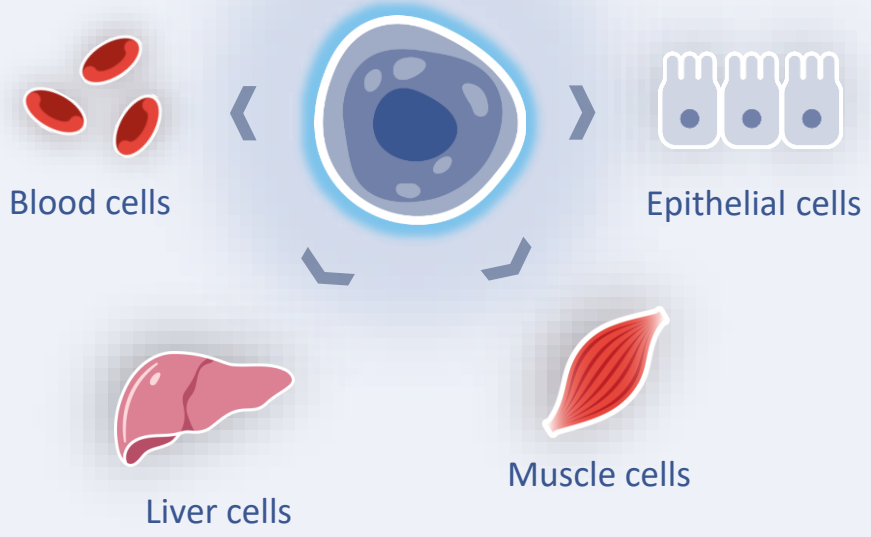
1. Siegel RL, et al. *CA Cancer J Clin*. 2026;76(1):e70043; 2. Halder S, et al. *Expert Opin Ther Targets*. 2023;27(4-5):305-324; 3. Hanahan D. *Cancer Discov*. 2022;12(1):31-46;
4. Torborg SR, et al. *Trends Cancer*. 2022;8(9):735-746; 5. Chhouri H, et al. *Cancers (Basel)*. 2023;15(2):504; 6. Zhou J, et al. *J Exp Clin Cancer Res*. 2021;40(1):328;
7. Carosi F, et al. *Crit Rev Oncol Hematol*. 2026;221:105207.

Chapter 2

Pathogenic Plasticity

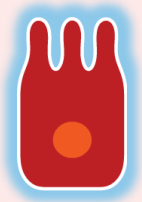
Plasticity Is a Normal Part of Tissue Homeostasis, but It Can Be Exploited by Cancer[1–3]

Adult Stem Cells



Adult stem cells throughout the body use plasticity to support normal homeostasis and injury repair[2–5]

Pathogenic Plasticity



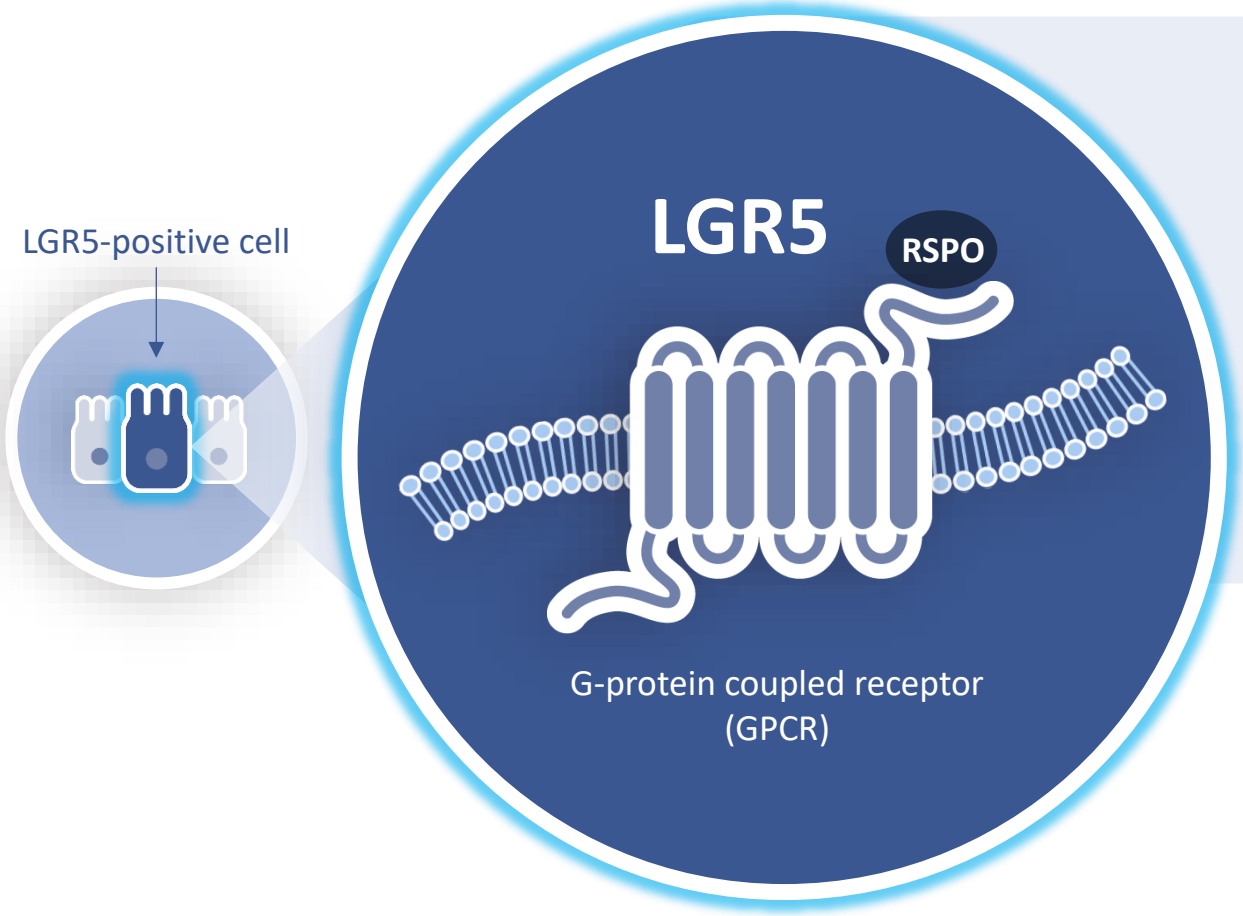
Epithelial cancer cell with plasticity

Tumor initiation | Resistance | Metastasis

Cancer cells that acquire plasticity can use it to initiate tumors, resist treatment, and drive metastasis[1–3]

1. Hanahan D. *Cancer Discov*. 2022;12(1):31-46; 2. Ge Y, Fuchs E. *Nat Rev Genet*. 2018;19(5):311-325; 3. Torborg SR, et al. *Trends Cancer*. 2022;8(9):735-746; 4. Brunet A, et al. *Nat Rev Mol Cell Biol*. 2023;24(1):45-62; 5. National Institutes of Health. Stem cell basics. Accessed April 2025. https://stemcells.nih.gov/info/basics/stc-basics.

In a Healthy Setting, Adult Stem Cells in Epithelial Tissue Express a Protein Called LGR5[1]



LGR5 is a receptor for R-spondins (RSPO), growth factors involved in tissue homeostasis[2,3]

RSPOs activate the Wnt/beta-catenin signaling pathway[4]

LGR5-positive cells support tissue regeneration[1]

In the intestine, LGR5-positive cells help replenish epithelial cells lost to shedding[4–6]

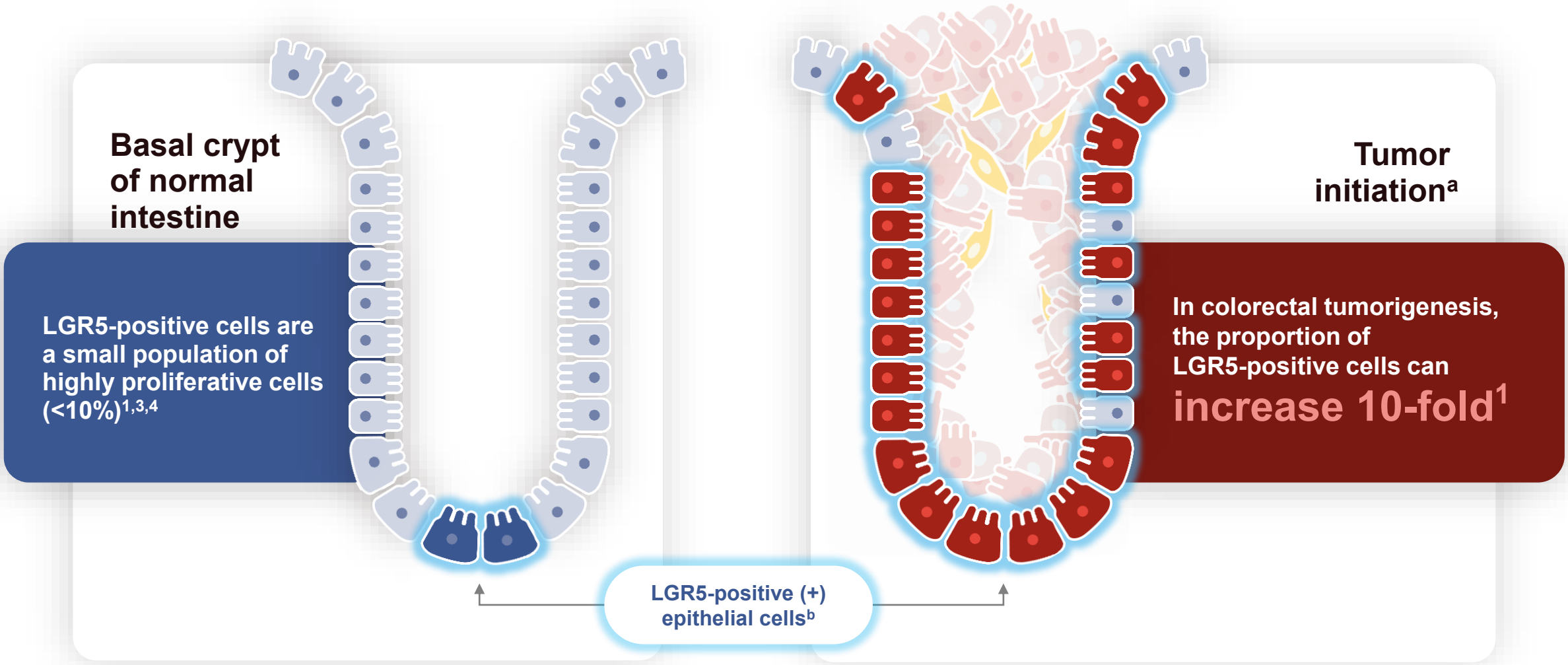
LGR5 is currently <u>not</u> an actionable biomarker[1,7]

LGR5 protein detection is possible for preclinical purposes (eg, western blot, live cell imaging),[8] but a suitable, well-validated antibody for human sample testing is not currently available[1,7]

LGR5, leucine-rich repeat-containing G-protein coupled receptor 5.

1. Leung C, et al. *Trends Cell Biol*. 2018;28(5):380-391; 2. Carmon KS, et al. *Proc Natl Acad Sci U S A*. 2011;108(28):11452-11457; 3. Nagano K. *Jpn Dent Sci Rev*. 2019;55(1):80-87;
4. de Lau W, et al. *Genes Dev*. 2014;28(4):305-316; 5. Barker N, et al. *Nature*. 2007;449(7165):1003-1007; 6. Barker N, et al. *Cell Stem Cell*. 2010;6(1):25-36;
7. Mueller N, et al. *Immunother Adv.* 2025;5(1):ltaf017; 8. High PC, et al. *Cell Rep Med.* 2025;6(10):102363.

In a Pathogenic Setting, Cancer Cells Unlock LGR5 Expression, Which Enables Tumor Initiation[1,2]



[a]Adenomas, and well and moderately differentiated adenocarcinomas[1,5]; [b]based on in situ hybridization (ISH) analysis of LGR5 mRNA expression.[1]

LGR5, leucine-rich repeat-containing G-protein coupled receptor 5; mRNA, messenger RNA.

1. Martin ML, et al. *Cell Signal*. 2018;42:97-105; 2. Leung C, et al. *Trends Cell Biol*. 2018;28(5):380-391; 3. de Lau W, et al. *Genes Dev*. 2014;28(4):305-316; 4. Barker N, et al. *Nature*. 2007;449(7165):1003-1007; 5. Dow LE, et al. *Cell*. 2015;161(7):1539-1552.

Overexpression of LGR5 Occurs Across Carcinomas and Has Been Associated With Poor Outcomes[1–6]

Colorectal cancer[3,4]

LGR5 overexpression was associated with:

- **~30%** Reduction in disease-free survival (DFS, 1 year)[3,a]
- **3×** Increase in liver metastasis[3]
- **3×** Increase in disease recurrence (5 year)[4,b]

Head and neck cancer[5]

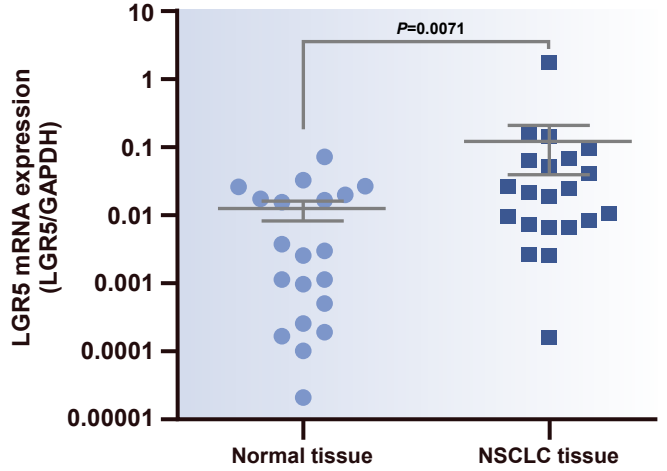
LGR5 overexpression was associated with[c]:

- ✓ **Worse disease-specific survival** (compared to low LGR5 expression)
- ✓ **Markers of EMT**

Each of these studies relies on mRNA expression for LGR5[3–6]

Lung cancer[6]

LGR5 overexpression observed in NSCLC tumor tissue



LGR5 expression in NSCLC tissues and matched adjacent normal tissues (N=22)

Used with permission from Nancy International Ltd, Subsidiary AME Publishing Company, Gao F, et al. The biological functions of LGR5 in promoting non-small cell lung cancer progression. *Transl Cancer Res*. 2019;8(1):203-211; permission conveyed through Copyright Clearance Center, Inc.

[a]Patients with CRC who underwent radical tumor resection[3]; [b]patients with CRC stage II[4]; [c]patients with oral squamous cell carcinoma (OSCC).[5]

CRC, colorectal cancer; EMT, epithelial-mesenchymal transition; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; H&N, head and neck cancer; LGR5, leucine-rich repeat-containing G-protein coupled receptor 5; mRNA, messenger RNA; NSCLC, non-small cell lung cancer; OSCC, oral squamous cell carcinoma.

1. Leung C, et al. *Trends Cell Biol*. 2018;28(5):380-391; 2. Xu L, et al. *Stem Cell Res Ther*. 2019;10(1):219; 3. Takahashi H, et al. *Ann Surg Oncol*. 2011;18(4):1166-1174; 4. Stanisavljević L, et al. *Acta Oncol*. 2016;55(12):1425-1433; 5. Rot S, et al. *BMC Cancer*. 2019;19(1):155; 6. Gao F, et al. *Transl Cancer Res*. 2019;8(1):203-211.

Pathogenic Plasticity

Key Takeaways

- **Plasticity** is a normal part of tissue homeostasis, but it can be **exploited by cancer**[1–3]
- Epithelial cancer **cells that express LGR5 acquire pathogenic plasticity**, which enables tumor initiation, proliferation, and metastasis[4,5]
- **Overexpression of LGR5** occurs across carcinomas and has been associated with **poor outcomes**[5–11,a]

[a]Outcomes data in NSCLC are based on immunohistochemical (antibody) detection; mRNA-based data correlating LGR5 expression with clinical outcomes were not included in the analysis.[11]

LGR5, leucine-rich repeat-containing G-protein coupled receptor 5; mRNA, messenger RNA; NSCLC, non-small cell lung cancer.

1. Hanahan D. *Cancer Discov*. 2022;12(1):31-46; 2. Ge Y, Fuchs E. *Nat Rev Genet*. 2018;19(5):311-325; 3. Torborg SR, et al. *Trends Cancer*. 2022;8(9):735-746; 4. Martin ML, et al. *Cell Signal*. 2018;42:97-105; 5. Leung C, et al. *Trends Cell Biol*. 2018;28(5):380-391; 6. Xu L, et al. *Stem Cell Res Ther*. 2019;10(1):219; 7. Takahashi H, et al. *Ann Surg Oncol*. 2011;18(4):1166-1174; 8. Stanisavljević L, et al. *Acta Oncol*. 2016;55(12):1425-1433; 9. Rot S, et al. *BMC Cancer*. 2019;19(1):155; 10. Gao F, et al. *Transl Cancer Res*. 2019;8(1):203-211; 11. Gao F, et al. *Biochem Biophys Res Commun*. 2015;462(2):91-98.

Chapter 3

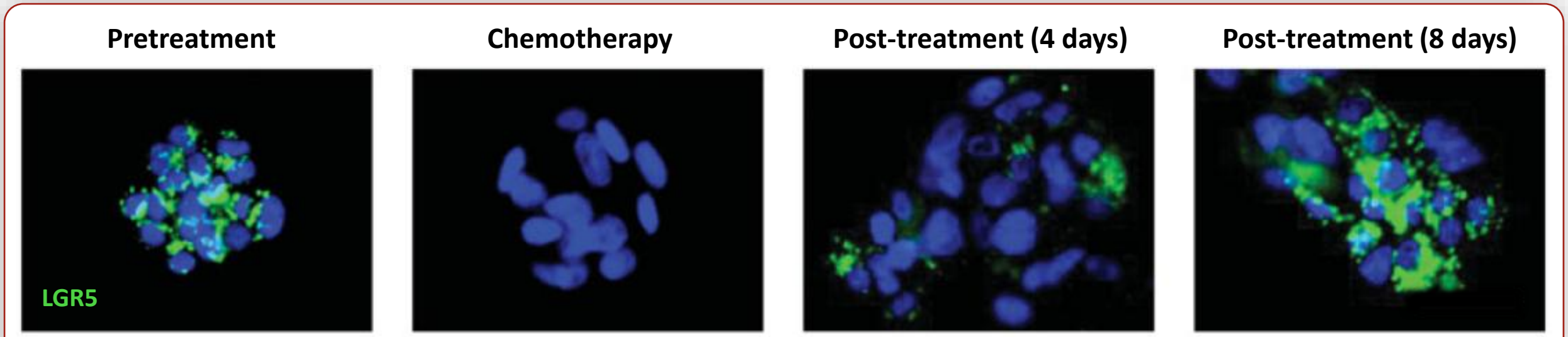
LGR5, the Moving Target

LGR5, leucine-rich repeat-containing G-protein coupled receptor 5.

Preclinical Data Indicate That Expression of LGR5 Is Dynamic and Changes in Response to Cancer Therapy[1–4]

1 of 2

LGR5 Expression Is Reduced by Chemotherapy[1]



Human colon cancer xenografts | Kobayashi S, et al. LGR5-positive colon cancer stem cells interconvert with drug-resistant LGR5-negative cells and are capable of tumor reconstitution. *Stem Cells*. 2012;30(12):2631-2644, by permission of Oxford University Press.

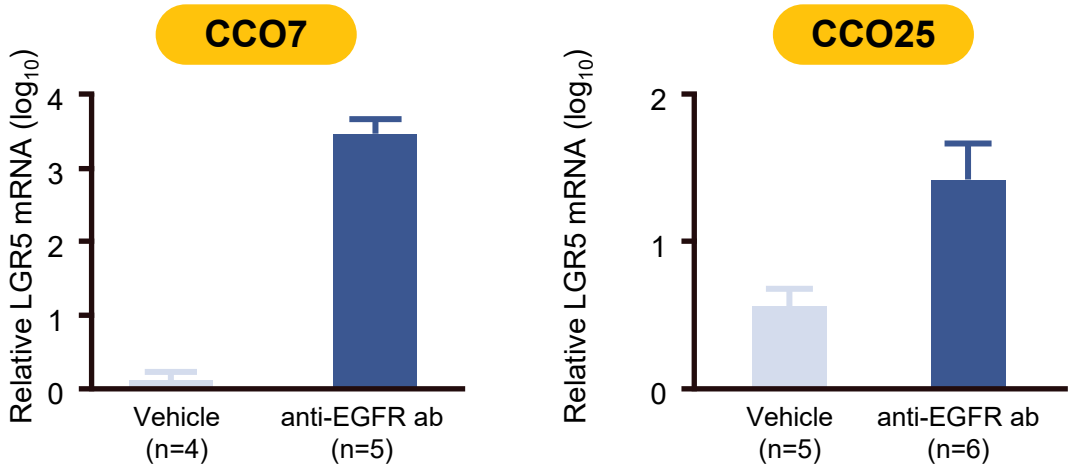
LGR5 expression can return in surviving cells and proliferative behavior can resume[1,2,5]

LGR5, leucine-rich repeat-containing G-protein coupled receptor 5.

1. Kobayashi S, et al. *Stem Cells*. 2012;30(12):2631-2644; 2. Posey TA, et al. *Mol Cancer Ther*. 2023;22(5):667-678; 3. Shimokawa M, et al. *Nature*. 2017;545(7653):187-192; 4. Basak O, et al. *Cell Stem Cell*. 2017;20(2):177-190.e4; 5. Fey SK, et al. *Cell Rep*. 2024;43(6):114270.

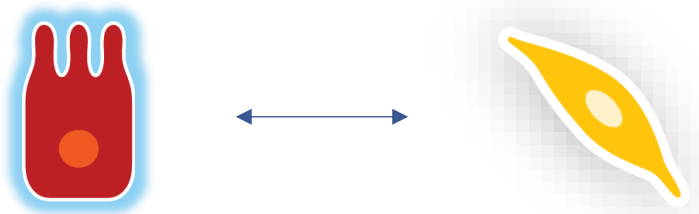
Preclinical Data Indicate That Expression of LGR5 Is Dynamic and Changes in Response to Cancer Therapy[1–4]

LGR5 expression is increased by EGFR-targeted therapy[3–5]



Reprinted from Shimokawa M, et al. Visualization and targeting of LGR5+ human colon cancer stem cells. *Nature*. 2017;545(7653):187-192, Copyright 2017, with permission from Springer Nature.

LGR5 expression fluctuates during EMT,[6–9] which is an EGFR resistance mechanism[10–14]



Epithelial cell
LGR5 positive
EGFR responsive

Mesenchymal cell
LGR5 negative
EGFR resistant

Is there a connection between LGR5 and resistance to EGFR-targeted therapy?[4]

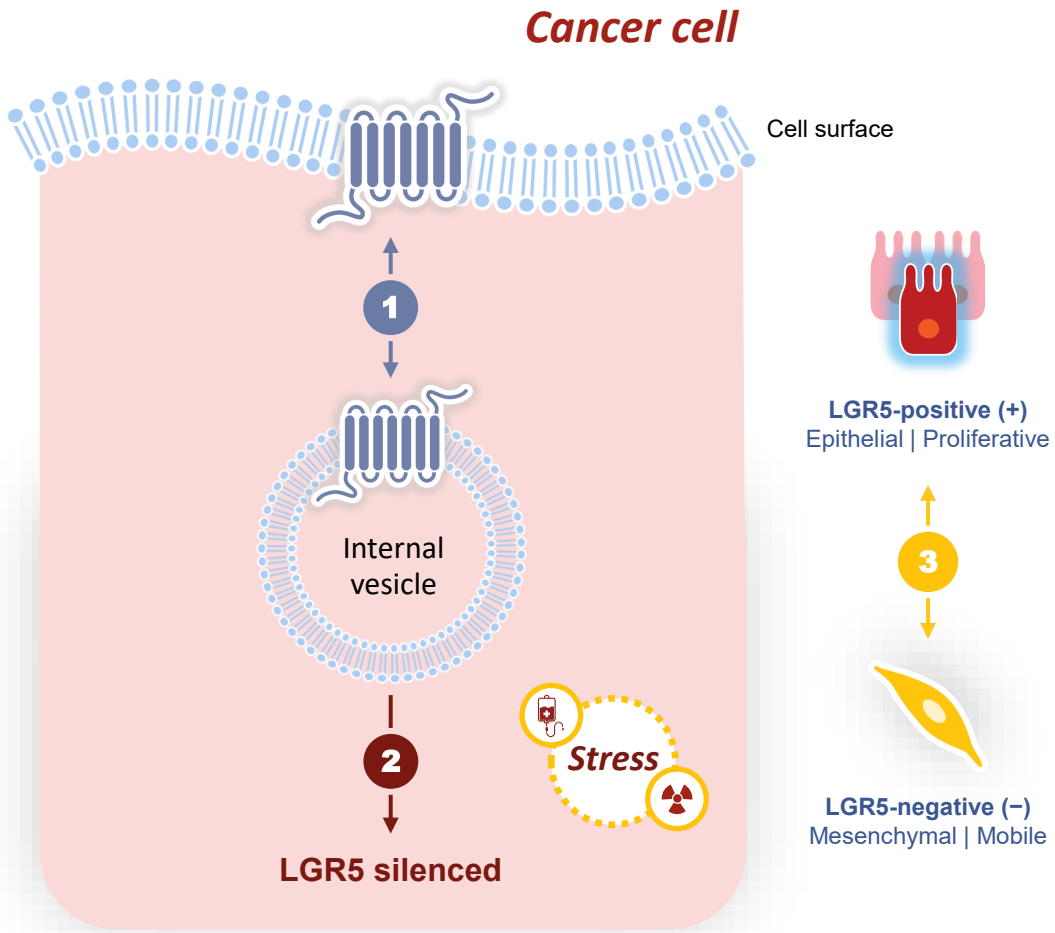
ab, antibody; CCO7 and CCO25, patient-derived colon cancer organoid models[3]; EGFR, epidermal growth factor receptor; EMT, epithelial-mesenchymal transition; LGR5, leucine-rich repeat-containing G-protein coupled receptor 5; mRNA, messenger RNA.

1. Kobayashi S, et al. *Stem Cells*. 2012;30(12):2631-2644; 2. Posey TA, et al. *Mol Cancer Ther*. 2023;22(5):667-678; 3. Shimokawa M, et al. *Nature*. 2017;545(7653):187-192; 4. Basak O, et al. *Cell Stem Cell*. 2017;20(2):177-190.e4; 5. High PC, et al. *Cell Rep Med.* 2025;6(10):102363; 6. Fumagalli A, et al. *Cell Stem Cell*. 2020;26(4):569-578.e7; 7. Conti S, et al. *Nat Commun*. 2024;15(1):3363; 8. Fey SK, et al. *Cell Rep.* 2024;43(6):114270; 9. Walker F, et al. *PLoS One.* 2011;6(7):e22733; 10. Chhouri H, et al. *Cancers (Basel).* 2023;15(2):504; 11. Zhou J, et al. *J Exp Clin Cancer Res*. 2021;40(1):328; 12. Carosi F, et al. *Crit Rev Oncol Hematol*. 2026;221:105207; 13. Thompson EW, et al. *Nat Rev Clin Oncol.* 2025;22(10):711-733; 14. Barr S, et al. *Clin Exp Metastasis*. 2008;25(6):685-693.

LGR5 Can Be a Dynamic Regulator of Pathogenic Plasticity[1–5]

Changes in Expression Drive Metastasis and Treatment Resistance[1–5]

1. LGR5 is constantly internalized (even without RSPO) and replaced at the cell surface[6,7]
2. LGR5 expression is silenced when cancer cells are subjected to stress (eg, chemotherapy, radiation)[4,8–11]
3. Transitioning between LGR5-positive and LGR5-negative states allows cancer cells to change phenotype and behavior[2–5,11–13]

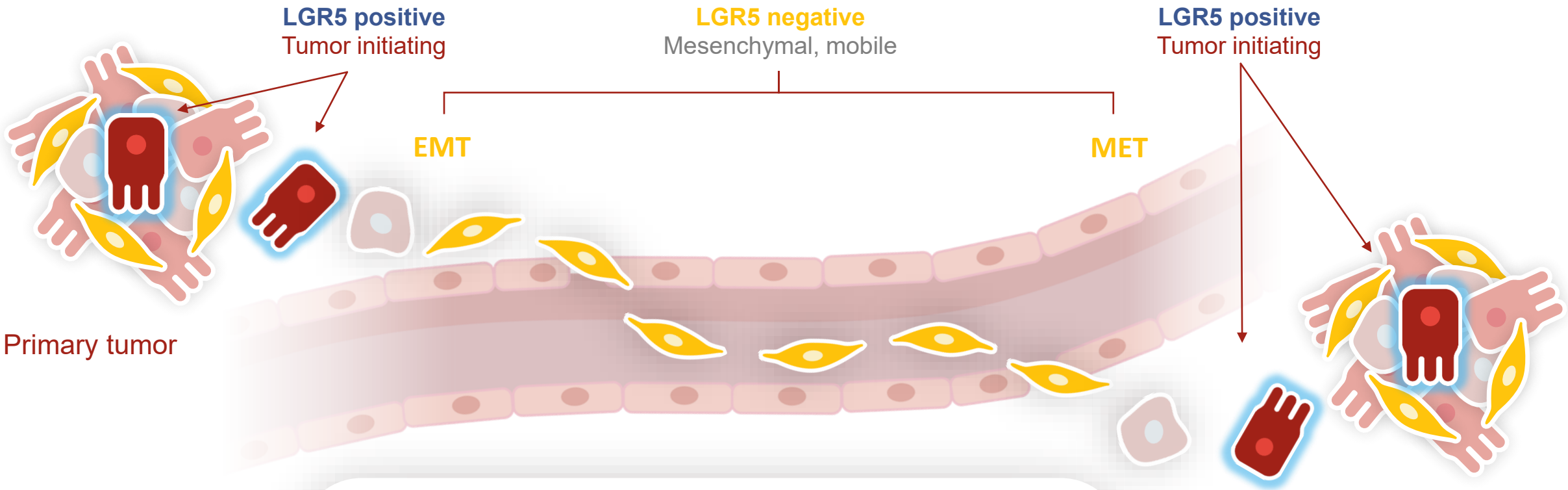


LGR5, leucine-rich repeat-containing G-protein coupled receptor 5; RSPO, R-spondins.

1. Morgan RG, et al. *Br J Cancer*. 2015;112(4):714-719; 2. Fumagalli A, et al. *Cell Stem Cell*. 2020;26(4):569-578.e7; 3. Walker F, et al. *PLoS One.* 2011;6(7):e22733; 4. Fey SK, et al. *Cell Rep.* 2024;43(6):114270; 5. Ge Y, Fuchs E. *Nat Rev Genet*. 2018;19(5):311-325; 6. Carmon KS, et al. *Mol Cell Biol*. 2012;32(11):2054-2064; 7. Snyder JC, et al. *J Biol Chem*. 2013;288(15):10286-10297; 8. Kobayashi S, et al. *Stem Cells*. 2012;30(12):2631-2644; 9. Posey TA, et al. *Mol Cancer Ther*. 2023;22(5):667-678; 10. Asfaha S, et al. *Cell Stem Cell.* 2015;16(6):627-638; 11. High PC, et al. *Trends Cancer*. 2026:S2405-8033(26)00037-3; 12. Conti S, et al. *Nat Commun*. 2024;15(1):3363; 13. Okamoto Y, et al. *J Biol Chem*. 2020;295(14):4591-4603.

In the Journey of Cancer, LGR5 Is Active During Tumor Initiation[1–3]

LGR5 is Silenced and Reactivated During Metastasis[2–6]



LGR5 is a moving target[7–10]

Developing an effective therapeutic strategy around LGR5 may require the integration of other targets or pathways[3,11–14]

EMT, epithelial-mesenchymal transition; LGR5, leucine-rich repeat-containing G-protein coupled receptor 5; MET, mesenchymal-epithelial transition.

1. Leung C, et al. *Trends Cell Biol*. 2018;28(5):380-391; 2. Fumagalli A, et al. *Cell Stem Cell*. 2020;26(4):569-578.e7; 3. High PC, et al. *Trends Cancer*. 2026:S2405-8033(26)00037-3; 4. Fey SK, et al. *Cell Rep.* 2024;43(6):114270; 5. Conti S, et al. *Nat Commun*. 2024;15(1):3363; 6. Walker F, et al. *PLoS One.* 2011;6(7):e22733; 7. Carmon KS, et al. *Mol Cell Biol*. 2012;32(11):2054-2064; 8. Snyder JC, et al. *J Biol Chem*. 2013;288(15):10286-10297; 9. Morgan RG, et al. *Br J Cancer*. 2015;112(4):714-719; 10. Okamoto Y, et al. *J Biol Chem*. 2020;295(14):4591-4603; 11. Shimokawa M, et al. *Nature*. 2017;545(7653):187-192; 12. Morgan RG, et al. *Br J Cancer*. 2018;118(4):558-565; 13. Xu L, et al. *Stem Cell Res Ther*. 2019;10(1):219; 14. Cao W, et al. *Nat Commun*. 2020;11(1):1961.

LGR5, the Moving Target

Key Takeaways

- Preclinical data indicate that **expression of LGR5 is dynamic** and **changes in response to cancer therapies** (eg, chemotherapy, radiation, EGFR targeted)[1–4]

- **LGR5 protein is constantly recycled** at the cell surface,[5,6] and this dynamic can be exploited by cancer cells to **regulate pathogenic plasticity, resist treatment, and metastasize**[1,2,7–14]

- Because **LGR5 is a moving target**,[5–8] developing an effective therapeutic strategy for it may require the **integration of other targets or pathways**[3,13,15–17]

EGFR, epidermal growth factor receptor; LGR5, leucine-rich repeat-containing G-protein coupled receptor 5.

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Thank You!

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