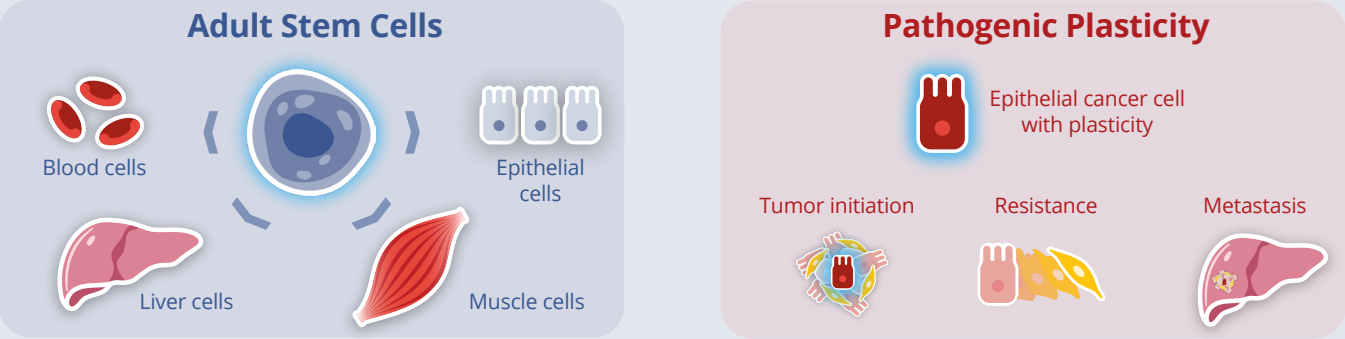
Pathogenic Plasticity

When Cancer Cells Acquire Pathogenic Plasticity, It Leads to Poor Patient Outcomes[1–4]

Visit www.cancerswildcard.com to learn more.

Plasticity Is a Normal Part of Tissue Homeostasis, but It Can Be Exploited by Cancer[1,2,5]

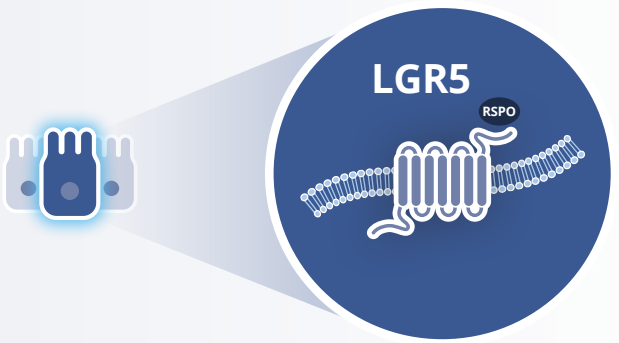
- **Plasticity:** characteristic of stem-like cells that enables self-renewal and differentiation into other cell phenotypes[5,6]
  - Plasticity is typically reserved for a small subset of cells throughout the body called adult stem cells[2,5,7,8]
  - Adult stem cells support normal homeostasis and injury repair (eg, cell replenishment)[2,5,7,8]
- **Pathogenic plasticity**: cancer cells co-opting plasticity to initiate tumors, metastasize, and resist treatment[5]
  - Cancer cells can hijack regenerative capabilities to drive disease progression[1,2,5]
  - Epithelial-mesenchymal transition (EMT) is an example of pathogenic plasticity that occurs in epithelial cancers[1,5,9,10,a]



[a]EMT is the process of epithelial cells losing their stationary characteristics (eg, cell-to-cell adhesion) and acquiring mesenchymal traits that facilitate motility and invasion.[9,11]

In a Healthy Setting, Adult Stem Cells in Epithelial Tissue Express a Protein Called LGR5[12]

- LGR5 is a receptor for R-spondins (RSPO), growth factors involved in tissue homeostasis[13,14]
  - RSPOs activate the Wnt/beta-catenin signaling pathway[15]
- **LGR5-positive cells support tissue regeneration[12]**
  - **In the intestine, LGR5-positive cells help replenish epithelial cells lost to shedding[15–17]**
- LGR5 is currently *not* an actionable biomarker[12,18]
  - LGR5 protein detection is possible for preclinical purposes (eg, western blot, live cell imaging),[19] but a suitable, well-validated antibody for human sample testing is not currently available[12,18]



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

Genmab

Visit www.cancerswildcard.com to learn more.

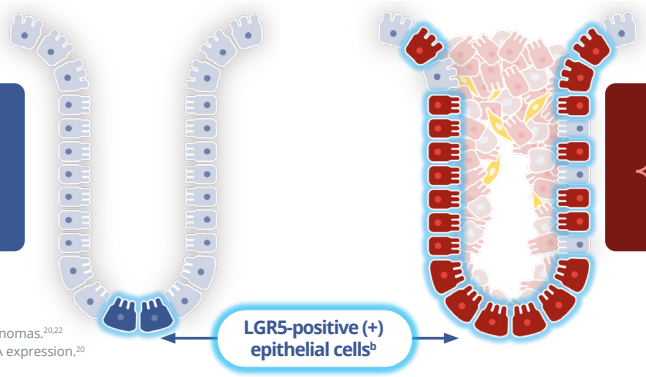
In a Pathogenic Setting, Cancer Cells Can Unlock LGR5 Expression, Which Enables Tumor Initiation[12,20]

Colorectal tumorigenesis

- LGR5-positive cells are normally a small population of cells (eg, <10% of basal crypt cells in the intestinal epithelium)[15,17,20]
- In the initial stages of colorectal tumorigenesis, the percentage of LGR5-positive cells has been shown to increase 10-fold (~70%),[20] which enables tumor cell proliferation and differentiation[12,18,21]
- LGR5 is a Wnt-target gene and oncogenic mutations in the Wnt/beta-catenin pathway can lead to increased expression of LGR5[18]

Basal crypt of normal intestine

LGR5-positive cells are a small population of highly proliferative cells (<10%)[15,17,20]



Tumor initiation[a]

In colorectal tumorigenesis, the proportion of LGR5-positive cells can increase 10-fold[20]

[a]Adenomas and well/moderately differentiated adenocarcinomas.[20,22]
[b]based on in situ hybridization (ISH) analysis of LGR5 mRNA expression.[20]

Overexpression of LGR5 Has Been Associated With Poor Outcomes[3,4,12,23–25]

- **In colorectal cancer (CRC),** LGR5 overexpression was associated with a ~30% reduction in disease-free survival (DFS; 1 year), a 3-fold increase in liver metastasis, and a 3-fold increase in disease recurrence (5 years)[3,23,a]
- **In head and neck cancer (H&N),** LGR5 overexpression was associated with worse disease-specific survival (compared to low LGR5 expression) and markers of epithelial-mesenchymal transition (EMT)[4,a]
- **In lung cancer (NSCLC),** LGR5 was overexpressed in tumor tissue compared with healthy adjacent tissue[24,a]

Overexpression of LGR5 has been associated with[a]

CRC[3,23]	H&N[4]	NSCLC[24]
• **Reduced DFS** • **Liver metastasis** • **Recurrence**	• **Worse disease-specific survival** (compared to low LGR5 expression) • **Markers of EMT[b]**	**Tumor tissue** (compared with healthy adjacent tissue)

[a]Evidence based on mRNA expression of LGR5.
[b]Mechanism of EGFR-treatment resistance.[26–28]
EGFR, epidermal growth factor receptor; EMT, epithelial-mesenchymal transition; mRNA, messenger RNA; NSCLC, non-small cell lung cancer.

See the full LGR5 story at CancersWildCard.com

1. Hanahan D. *Cancer Discov*. 2022;12(1):31-46; **2.** Ge Y, Fuchs E. *Nat Rev Genet*. 2018;19(5):311-325; **3.** Takahashi H, et al. *Ann Surg Oncol*. 2011;18(4):1166-1174; **4.** Rot S, et al. *BMC Cancer*. 2019;19(1):155; **5.** Torborg SR, et al. *Trends Cancer*. 2022;8(9):735-746; **6.** Du X, et al. *Front Cell Dev Biol*. 2026;14:1752590; **7.** National Institutes of Health. Stem cell basics. Accessed March 2026. https://stemcells.nih.gov/info/basics/stc-basics; **8.** Brunet A, et al. *Nat Rev Mol Cell Biol*. 2023;24(1):45-62; **9.** Makitie AA, et al. *Head Neck*. 2019;41(10):3712-3718; **10.** Strauss R, et al. *Mol Ther*. 2012;20(5):887-897; **11.** Thompson EW, et al. *Nat Rev Clin Oncol*. 2025;22(10):711-733; **12.** Leung C, et al. *Trends Cell Biol*. 2018;28(5):380-391; **13.** Carmon KS, et al. *Proc Natl Acad Sci U S A*. 2011;108(28):11452-11457; **14.** Nagano K. *Jpn Dent Sci Rev*. 2019;55(1):80-87; **15.** de Lau W, et al. *Genes Dev*. 2014;28(4):305-316; **16.** Barker N, et al. *Cell Stem Cell*. 2010;6(1):25-36; **17.** Barker N, et al. *Nature*. 2007;449(7165):1003-1007; **18.** Mueller N, et al. *Immunother Adv*. 2025;5(1):ltaf017; **19.** High PC, et al. *Cell Rep Med*. 2025;6(10):102363; **20.** Martin ML, et al. *Cell Signal*. 2018;42:97-105; **21.** Barker N, et al. *Nature*. 2009;457(7229):608-611; **22.** Dow LE, et al. *Cell*. 2015;161(7):1539-1552; **23.** Stanisavljevic L, et al. *Acta Oncol*. 2016;55(12):1425-1433; **24.** Gao F, et al. *Transl Cancer Res*. 2019;8(1):203-211; **25.** Xu L, et al. *Stem Cell Res Ther*. 2019;10(1):219; **26.** Carosi F, et al. *Crit Rev Oncol Hematol*. 2026;221:105207; **27.** Chhouri H, et al. *Cancers (Basel)*. 2023;15(2):504; **28.** Zhou J, et al. *J Exp Clin Cancer Res*. 2021;40(1):328.

Genmab