Cancer is a common name for several distinct diseases caused by uncontrolled cell growth and proliferation. More than 200 types of cancer are described in the literature, each of them with its own identity given by specific gene, protein or hormone signatures. However, concerted and redundant dysregulations of mitogenic pathways arising from growth factor receptors (GFRs) are common events in all cancer types [1,2].

These sophisticated membrane-spanning proteins harmonize the information flow from several sources, controlling the mitogenic network in the normal cell. The complexity of GFRs function is supported by their multiple regulatory mechanisms, including feedback loops, multidirectional cross-communication and redundancy in downstream signalling. Recent large-scale studies identified alterations in genes and proteins of several GFRs such as epidermal growth factor receptor (EGFR), platelet-derived growth factor receptor α/β (PDGFR α/β), vascular endothelial growth factor receptors (VEGFRs), IGF-1R, fibroblast growth factor receptor (FGFR), etc. [3].

The majority of malignant diseases are related to aberrant intra- and intercellular communication, associated with subverted GFRs pathways. At the molecular level, the overactivation of GFRs induces a mitogenic response and maintains cancer cell growth. Four main mechanisms are known to generate aberrant activation of GFRs in malignant diseases: autocrine/paracrine activation, genomic amplification, chromosomal rearrangements and gain-of-function mutations [4,5].

GFs mediate their mitogenic function by binding to and activating GFRs with intrinsic tyrosine kinase (TKs) activity. Cancer cells produce GFs or reprogram and force other cells to produce GFs according to their own needs, becoming independent of endocrine signalling and finally leading to constitutive receptors activation in tumours [6–8].

GFRs gene amplification, also known as genomic DNA copy number amplification, has been found in a wide variety of tumours, causing receptor protein upregulation and overactivation, inducing oncogenic behaviour and resistance to therapy [9,10].

Chromosome rearrangements mechanism is a usual condition of malignant cells, in which a fragment of chromosomes is deleted or inverted, giving rise to fusion proteins that are responsible for the formation of several types of malignancies. The BCR-ABL fusion oncprotein, which fuses the ABL1 tyrosine kinase gene on chromosome 9 to the BCR gene on chromosome 22, was the first tyrosine kinase fusion identified [11]. Chromosome rearrangements leading to fusion proteins are also found in many solid cancers, such as breast cancer, brain tumours, lung cancer, colorectal cancer, etc. [12–15].

Gain-of-function mutations can exercise mitogenic functions by stimulation of growth factors or by inducing constitutive activation of GFRs, driving uncontrolled cell proliferation and tumour progression [16].

Once activated, GFRs trigger a wave of intracellular signalling events, mediated by two major pathways: mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinases (PI3K) cascades [17].

Many intracellular proteins involved in rat sarcoma virus (RAS)/MAPK or PI3K/AKT pathways can also function as oncogenes. Mutations affecting key proteins in RAS/MAPK
or PI3K/AKT pathways are known to be crucial in maintaining the malignancy of different types of cancers [18–20].

Many effector proteins in GFRs signal transduction, such as PI3K, extracellular signal-regulated kinase 1/2 (ERK1/2) or MAPK can act as junction for multiple signalling pathways [21]. It is also well demonstrated that mutations in mammalian target of rapamycin (mTOR), RAS or rapidly accelerated fibrosarcoma (RAF) are very common in malignant diseases [22].

Crosstalk and collaboration between GFRs and other protein families are constantly being discovered, making the receptor signalling system far more complex. For example, G protein-coupled receptors (GPCRs) can engage GFRs to mediate cell proliferation, differentiation, and vice versa, several GFs use GPCRs proteins to exert their mitogenic signal signalling [23].

Moreover, the evasion of apoptotic signals and the requirement of angiogenesis were also found to be of fundamental importance for tumour progression and metastasis. In this context, high expression of GFRs aids blood vessel formation, cell migration and the inhibition of apoptosis [24,25].

All this information has guided the development of compounds, designed to target one or more of these pathways in cancer cells. A vast variety of GFR signalling inhibitors have been developed, many of which have been approved by the Food and Drug Administration (FDA). While some FDA-approved inhibitors are selective for individual GFRs (e.g., Alectinib, Afatinib, Dacomitinib, Erlotinib, Gefitinib, Lapatinib, etc.), others demonstrate efficiency by inhibiting several receptors (e.g., Dasatinib, Lestauninib, Imatinib, Ponatinib, Vandetanib, etc.). However, the development of novel therapeutic strategies for cancer treatment is tightly restricted by the similarities between the normal and malignant cells. GFR-directed therapy that would theoretically selectively kill malignant cells and reduce the toxicity associated with nonselective conventional chemotherapy may be a promising treatment for cancer. Based on this rationale, different strategies have been developed to inhibit the oncogenic effects of GFRs (e.g., small-molecule inhibitors, monoclonal antibodies, siRNA, antisense oligodeoxynucleotides, triple helix, dominant-negative mutants, etc.).

This Special Issue will cover the latest preclinical and clinical progress made in the areas associated with GFRs' oncogenic signalling.

**Funding:** Grant PN-III-P4-ID-PCE2020-1649, by the UEFISCDI Authority, Romania.

**Conflicts of Interest:** The author declares no conflict of interest.

**References**

1. Mongre, R.K.; Mishra, C.B.; Shukla, A.K.; Prakash, A.; Jung, S.; Ashraf-Uz-Zaman, M.; Lee, M.S. Emerging Importance of Tyrosine Kinase Inhibitors against Cancer: Quo Vadis to Cure? *Int. J. Mol. Sci.* **2021**, *22*, 11659. [CrossRef] [PubMed]

2. Carapancea, M.; Alexandru, O.; Fetea, A.S.; Dragutescu, L.; Castro, J.; Georgescu, A.; Popa-Wagner, A.; Bäcklund, M.L.; Lewensohn, R.; Dricu, A. Growth factor receptors signaling in glioblastoma cells: Therapeutic implications. *J. Neurooncol.* **2009**, *92*, 137–147. [CrossRef] [PubMed]

3. Wang, Z.; Zhang, L.; Xu, W.; Li, J.; Li, Y.; Zeng, X.; Zhong, M.; Zhu, Y. The Multi-Omics Analysis of Key Genes Regulating EGFR-TKI Resistance, Immune Infiltration, SCLC Transformation in EGFR-Mutant NSCLC. *J. Inflamm. Res.* **2022**, *15*, 649–667. [CrossRef]

4. Chioni, A.M.; Grose, R.P. Biological Significance and Targeting of the FGFR Axis in Cancer. *Cancers* **2021**, *13*, 5681. [CrossRef]

5. Dricu, A.; Kanter, L.; Wang, M.; Nilsson, G.; Hjerdtman, M.; Wejde, J.; Larsson, O. Expression of the insulin-like growth factor 1 receptor (IGF-1R) in breast cancer cells: Evidence for a regulatory role of dolichyl phosphate in the transition from an intracellular to an extracellular IGF-1 pathway. *Glycobiology* **1999**, *9*, 571–579. [CrossRef] [PubMed]

6. Singh, A.B.; Harris, R.C. Autocrine, paracrine and juxtacrine signaling by EGFR ligands. *Cell Signal.* **2005**, *17*, 1183–1193. [CrossRef] [PubMed]

7. Walsh, J.H.; Karnes, W.E.; Cuttitta, F.; Walker, A. Autocrine growth factors and solid tumor malignancy. *West J. Med.* **1991**, *155*, 152–163.

8. Kentsis, A.; Reed, C.; Rice, K.L.; Sanda, T.; Rodig, S.J.; Tholoulou, E.; Christie, A.; Valk, P.J.; Delwel, R.; Ngo, V.; et al. Autocrine activation of the MET receptor tyrosine kinase in acute myeloid leukemia. *Nat. Med.* **2012**, *18*, 1118–1122. [CrossRef]
9. Hechtman, J.F.; Polydorides, A.D. HER2/neu gene amplification and protein overexpression in gastric and gastroesophageal
juncture adenocarcinoma: A review of histopathology, diagnostic testing, and clinical implications. *Arch. Pathol. Lab. Med.* 2012,
136, 691–697. [CrossRef]

10. Yu, H.A.; Arcila, M.E.; Rekhtman, N.; Sima, C.S.; Zakowski, M.F.; Pao, W.; Kris, M.G.; Miller, V.A.; Ladanyi, M.; Riely, G.J. Analysis
of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. *Clin.
Cancer Res.* 2013, 19, 2240–2247. [CrossRef]

11. Spiers, A.S. The clinical features of chronic granulocytic leukaemia. *Clin. Haematol.* 1977, 6, 77–95. [CrossRef]

12. Han, T.; Schatoff, E.M.; Murphy, C.; Zafra, M.P.; Wilkinson, J.E.; Elemento, O.; Dow, L.E. R-Spondin chromosome rearrangements
drive Wnt-dependent tumour initiation and maintenance in the intestine. *Nat. Commun.* 2017, 8, 15945. [CrossRef] [PubMed]

13. Stransky, N.; Cerami, E.; Schal, M.; Kim, J.L.; Lengauer, C. The landscape of kinase fusions in cancer. *Nat. Commun.* 2014, 5, 4846.
[CrossRef] [PubMed]

14. Wang, M.; Nilsson, G.; Carlberg, M.; Dricu, A.; Wejde, J.; Kreicbergs, A.; Larsson, O. Specific and sensitive detection of the
EWS/FLI1 fusion protein in Ewing’s sarcoma by Western blotting. *Virchows Arch.* 1998, 432, 131–134. [CrossRef]

15. Mitelman, F.; Johansson, B.; Mertens, F. The impact of translocations and gene fusions on cancer causation. *Nat. Rev. Cancer*
2007, 7, 233–245. [CrossRef] [PubMed]

16. Isozaki, K.; Hirota, S. Gain-of-Function Mutations of Receptor Tyrosine Kinases in Gastrointestinal Stromal Tumors. *Curr. Genom.*
2006, 7, 469–475. [CrossRef]

17. Schlessinger, J. Common and distinct elements in cellular signaling via EGF and FGF receptors. *Science* 2004, 306, 1506–1507.
[CrossRef]

18. Downward, J. Targeting RAS signalling pathways in cancer therapy. *Nat. Rev. Cancer* 2003, 3, 11–22. [CrossRef]

19. Zhang, J.; Grubor, V.; Love, C.L.; Banerjee, A.; Richards, K.L.; Mieczkowski, P.A.; Dunphy, C.; Choi, W.; Au, W.Y.; Srivastava, G.;
et al. Genetic heterogeneity of diffuse large B-cell lymphoma. *Proc. Natl. Acad. Sci. USA* 2013, 110, 1398–1403. [CrossRef]

20. Stern, D.F. Keeping Tumors Out of the MAPK Fitness Zone. *Cancer Discov.* 2018, 8, 20–23. [CrossRef]

21. Dhillon, A.S.; Hagan, S.; Rath, O.; Kolch, W. MAP kinase signalling pathways in cancer. *Oncogene* 2007, 26, 3279–3290. [CrossRef] [PubMed]

22. Ambrogio, C.; Kühler, J.; Zhou, Z.W.; Wang, H.; Paranal, R.; Li, J.; Capelletti, M.; Caffarri, C.; Li, S.; Lv, Q.; et al. KRAS
Dimerization Impacts MEK Inhibitor Sensitivity and Oncogenic Activity of Mutant KRAS. *Cell* 2018, 172, 857–868.e15. [CrossRef]

23. Cattaneo, F.; Guerra, G.; Parisi, M.; De Marinis, M.; Tafuri, D.; Cinelli, M.; Ammendola, R. Cell-surface receptors transactivation
mediated by g protein-coupled receptors. *Int. J. Mol. Sci.* 2014, 15, 19700–19728. [CrossRef] [PubMed]

24. Neophytou, C.M.; Trougakos, I.P.; Erin, N.; Papageorgis, P. Apoptosis Deregulation and the Development of Cancer Multi-Drug
Resistance. *Cancers* 2021, 13, 4363. [CrossRef] [PubMed]

25. Serban, F.; Artene, S.A.; Georgescu, A.M.; Purcaru, S.O.; Tache, D.E.; Alexandru, O.; Dricu, A. Epidermal growth factor, latrophilin,
and seven transmembrane domain-containing protein 1 marker, a novel angiogenesis marker. *Onco Targets Ther.* 2015, 8, 3767–3774.
[CrossRef] [PubMed]