Insulin-Like Growth Factor System

Subjects: Cell Biology

Contributor: Caterina Mancarella, Katia Scotlandi

Aberrant bioactivity of the insulin-like growth factor (IGF) system results in the development and progression of several pathologic conditions including cancer. Preclinical studies have shown promising anti-cancer therapeutic potentials for anti-IGF targeted therapies. However, a clear but limited clinical benefit was observed only in a minority of patients with sarcomas. The molecular complexity of the IGF system, which comprises multiple regulators and interactions with other cancer-related pathways, poses a major limitation in the use of anti-IGF agents and supports the need of combinatorial therapeutic strategies to better tackle this axis.

Keywords: IGF system ; sarcomas ; IGF inhibitors ; Ephrin receptors ; Hippo pathway ; BET proteins ; CXCR4 signaling ; combined treatments

1. Introduction

The IGF system regulates a variety of physiological processes including aging, glucose metabolism, growth, and differentiation [1][2][3]. Alterations in IGF equilibrium result in different pathologies including endocrine disorders, skin diseases and cancer [3][4]. Accordingly, multiple anti-IGF targeted therapies were developed and tested in different tumor types [5] but, in spite of encouraging preclinical results, clinical studies have been largely disappointing [6]. Excellent reviews have recently discussed patients' response to IGF inhibitors [5][7][8]. Notably, among solid tumors, a few but significant achievements were obtained in sarcomas, particularly in Ewing sarcoma [5][6][8][9]. Major factors limiting the efficacy of anti-IGF1R therapy in the clinic include (i.) the lack of validated biomarkers of response for patient selection; (ii.) the development of primary and/or acquired resistance, with absence of significant activity of anti-IGF agents particularly as monotherapy; (iii.) underestimation of the molecular complexity surrounding the IGF axis [6][9]. The variety of biological responses elicited by the IGFs is not solely depending on its canonical components but it also relies on functional cross-talks integrating signals from other factors [2]. The IGF system is finely tuned by a variety of growth factors and hormones [2], post-transcriptional regulators like RNA-binding proteins and non-coding RNAs [9][10][11][12]. The IGF system also interacts with other pathways, including EGFR, HER2, cMET, ALK, or functional partners, like DDR1, E-cadherin, decorin, leading to signaling redundancy or compensatory activity [6][9][12]. To date, combinatorial therapy with anti-IGFs agents represents an attractive therapeutic option.

2. Therapeutic Approaches to Block the IGF System

Three major therapeutic approaches have been developed to block the IGF system: (i.) anti-IGF1R monoclonal antibodies (mAbs); (ii.) tyrosine kinase inhibitor small molecules; (iii.) IGFs neutralizing antibodies and ligands TRAP. A major limitation in the use of these agents is still the lack of a clear rationale in patient recruitment, which may have significantly contributed to poor clinical results. Accordingly, most of the studies were performed in unselected patients further demonstrating that identification of predictive biomarkers to guide patients' selection still represents an urgent need to optimize the use of anti-IGF agents [6].

2.1. Anti-IGF1R mAbs

mAbs against the IGF1R not only block the binding of IGFs to IGF1R but also downregulate IGF1R levels by inducing receptor internalization and degradation, thereby inhibiting receptor downstream signaling [13][14][15]. The first anti-IGF1R mAb αIR3 showed efficacy in preclinical studies by inhibiting cancer cells' growth both in vitro and in vivo [16]. Several mAbs have been subsequently developed and promising preclinical results were obtained in different tumor models with figitumumab (CP-751871) [17], teprotumumab (R1507) [18], cixutumumab (IMC-A12) [19], dalotuzumab (MK-0646) [20], ganitumab (AMG 479) [21], robatumumab (MK-7454) [22]. However, subsequent clinical trials results were disappointing due to the onset of adverse dose-limiting side effects and lack of antitumor activity in most tumor types. Excellent reviews have recently summarized the results of clinical trials using anti-IGF agents [5][7][8].

Of note, hyperglicemia represents the major side effect correlated with the use of IGF1R mAbs [23]. Indeed, in spite of lack of activity against the IR, some mAbs induce ligand-independent internalization and degradation of IGF1R/IR-A and IGF1R/IR-B hybrids, causing insulin resistance [15][23][24]. In addition, IGF1R blockade might also determine the dysregulation of IGF1R/IGF1/GH, which might determine the inhibition of IGF1 hypoglycemic effect and/or a compensatory increase in circulating GH, leading to increased liver glucogenesis and insulin resistance [23].

The compensatory activation of other RTKs is a common mechanism by which tumor cells develop intrinsic or acquired resistance, thus limiting the antitumor effects of these agents. A phase II study evaluating the efficacy and toxicity of figitumumab in patients with squamous cell carcinoma of the head and neck reported a 41% incidence of hyperglycemia and no clinically significant activity of the mAb in patients [23]. Importantly, molecular analysis conducted in these patients indicated that downregulation of IGF1R levels were associated with a concomitant activation of the PI3K/Akt and MAPK pathways due to compensatory upregulation of the epidermal growth factor receptor (EGFR) [23]. Similarly, compensatory activation of the IR-A and IR-B by insulin and IGF2 [13][25], activation of HER3/AKT pathway, or the induction of a mesenchymal–epithelial transition factor (c-MET) all contribute in conferring resistance to anti-IGF1R mAbs [26][27].

Ganitumab and teprotumumab are currently being tested in clinical trials. Importantly, due to overall lack of IGF1R mAbs efficacy as monotherapy, ganitumab is being tested in combination with other drugs including the Src family knase (SFK) inhibitor dasatinib (NCT03041701), the CDK4/6 inhibitor palbociclib (NCT04129151), and metformin (NCT01042379). An ongoing phase I trial is testing the efficacy of microdevice delivery of different compounds, including ganitumab, in sarcomas (NCT04199026). Teprotumumab is being tested in clinical trials in non-malignant disorders [4]. Despite the fact that the clinical development of cixutumumab has been terminated, cixutumumab conjugated with PEGylated maytansine shows promising in vitro results [28]. Interestingly, an ongoing clinical trial (NCT03316638) is currently testing clinical safety and maximum tolerated dose (MTD) of W0101, a unique IGF1R—targeted antibody—drug conjugate, designed to deliver a cytotoxic auristatin derivative to IGF1R overexpressing tumor cells [29]. Preclinical studies demonstrated the antitumor activity of W0101 and the specificity of this compound for IGF1R and the absence of binding to IR, which should limit potential side effects related to insulin pathway [29].

2.2. Tyrosine Kinase Inhibitor Small Molecules

Several tyrosine kinase inhibitor (TKI) small molecules were developed to target the kinase activity of the IGF1R. These agents are divided into ATP-competitive and non-ATP-competitive inhibitors, depending on the ability to block the ATP binding cleft. Based on the high sequence homology between the IGF1R and the IR kinase domains, particularly in the ATP binding cleft (100%) [30], ATP-competitive inhibitors including linsitinib (OSI-906) [31] and BMS-754804 [32], inhibit both the IGF1R and the IR. Despite promising preclinical results, indicating in vitro antiproliferative effects and in vivo antitumor efficacy [31][32], disappointing outcomes were obtained in the clinical setting. While inhibiting both the IGF1R and the IR-A might represent an advantage to avoid compensatory mechanisms in tumor cells, blockade of the IR-B compromises glucose metabolism. None of these compounds are currently under evaluation in the clinic.

Non-ATP-competitive inhibitors, such as the cyclolignan picropodophyllin (PPP; AXL1717), interact with the substrate binding site, thus inhibiting IGF1R signaling without affecting IR action [33]. In preclinical studies, PPP inhibited cell growth and induced cell death in different tumor types [33][34]. In clinical trials, AXL1717, an orally available small molecule whose active agent is PPP, displayed a good safety profile but limited anti-tumor activity. In a phase I trial AXL1717 determined prolonged stable disease in 44% of astrocytoma patients and it caused reversible neutropenia as a major side effect [35]. On the other side, a phase II study in non-small cell lung cancer (NSCLC) patients comparing the efficacy of AXL1717 to docetaxel indicated that no treatment was better than the other in treating locally advanced or metastatic NSCLC [36]. Still, the lower incidence of neutropenia in the AXL1717-treated group confirmed the tolerability of this drug, thus warranting further research [36].

2.3. IGFs Neutralizing Antibodies and Ligands TRAP

Neutralizing IGFs ligands represents an alternative therapeutic strategy to block the IGF system. MEDI-573 is a fully human monoclonal antibody that neutralizes both IGF1 and IGF2 and inhibits both IGF1R and IR-A downstream signaling without affecting insulin-dependent IR activation [37]. Preclinical results obtained in embryonic fibroblast cell lines overexpressing the IGF1R and IGF1/IGF2 or IR-A demonstrated that MEDI-573 inhibits in vivo growth in xenograft models [37]. Recent preclinical evidence demonstrated that MEDI-573 induces apoptosis and inhibits tumor growth in a subset of colorectal cancer overexpressing IGF2 [38]. In clinical trials, MEDI-573 determined antitumor activity in advanced solid tumors as shown by stable disease (around 33% of patients), and a favorable tolerability profile without affecting metabolic homeostasis [39].

Among the IGF-targeting strategies, an emerging area of research is currently focusing on IGF-Trap. The IGF-Trap is a heterotetramer, composed of the extracellular domain of the IGF1R fused to the Fc portion of human IgG1 [40][41]. The IGF-Trap binds IGF1 and IGF2 with higher affinity than insulin, thus avoiding metabolic effects [40][41]. In addition, it inhibits IGF1R-driven cellular functions such as migration, proliferation and survival in various carcinoma cellular models [40][41]. The IGF-Trap significantly reduces metastatic spread of colon and lung carcinoma cells to the liver, representing a novel promising alterative to IGF1R or IGF1/IGF2 antibodies [40][41].

3. Conclusions

Dysregulation of the IGF system drives cancer cell proliferation, migration, EMT, and drug resistance. Accordingly, multiple anti-IGF therapeutic strategies have been developed to block this pathway, including IGF1R monoclonal antibodies, tyrosine-kinase inhibitors, IGFs neutralizing antibodies or the new IGF-TRAP and IGF1R—targeted antibody—drug conjugates. After decades of research in the field, clinical relevance of therapeutic agents targeting the IGF system in cancer appears limited to subsets of sarcomas. This is in line with the exceptional dependence of these diseases on IGF-driven processes. Still, even in those tumors, molecular profiling to identify patients who would better respond to anti-IGF-based treatment is still an urgent clinical need. In addition, any therapeutic strategy solely targeting the IGF axis is likely insufficient to block tumor growth. The majority of the information obtained to date shows the complexity of the IGF axis regulation and the multiplicity of interactions with other cancer-relevant pathways, which either potentiate or compensate molecular signaling mediated by the IGF system. A better understanding of this network of signaling pathways might contribute to the identification of novel and more effective therapeutic combinations for sarcoma treatment.

References

1. Stanley, T.L.; Fourman, L.T.; Zheng, I.; McClure, C.M.; Feldpausch, M.N.; Torriani, M.; Corey, K.E.; Chung, R.T.; Lee, H.; Kleiner, D.E.; et al. Relationship of IGF-1 and IGF-Binding Proteins to Disease Severity and Glycemia in Nonalcoholic Fatty Liver Disease. J. Clin. Endocrinol. Metab. 2021, 106, e520–e533.
2. Hakuno, F.; Takahashi, S.I. IGF1 receptor signaling pathways. J. Mol. Endocrinol. 2018, 61, T69–T86.
3. Frystyk, J.; Teran, E.; Gude, M.F.; Bjerre, M.; Hjortebjerg, R. Pregnancy-associated plasma proteins and Stanniocalcin-2—Novel players controlling IGF-I physiology. Growth Horm. IGF Res. Off. J. Growth Horm. Res. Soc. Int. IGF Res. Soc. 2020, 53–54, 101330.
4. Osher, E.; Macaulay, V.M. Therapeutic Targeting of the IGF Axis. Cells 2019, 8, 895.
5. de Groot, S.; Rottgering, B.; Gelderblom, H.; Pijl, H.; Szuhai, K.; Kroep, J.R. Unraveling the Resistance of IGF-Pathway Inhibition in Ewing Sarcoma. Cancers 2020, 12, 3568.
6. Simpson, A.; Petnga, W.; Macaulay, V.M.; Weyer-Czernilofsky, U.; Bogenrieder, T. Insulin-Like Growth Factor (IGF) Pathway Targeting in Cancer: Role of the IGF Axis and Opportunities for Future Combination Studies. Target. Oncol. 2017, 12, 571–597.
7. Cao, J.; Yee, D. Disrupting Insulin and IGF Receptor Function in Cancer. Int. J. Mol. Sci. 2021, 22, 555.
8. Hua, H.; Kong, Q.; Yin, J.; Zhang, J.; Jiang, Y. Insulin-like growth factor receptor signaling in tumorigenesis and drug resistance: A challenge for cancer therapy. J. Hematol. Oncol. 2020, 13, 64.
9. Mancarella, C.; Scotlandi, K. IGF system in sarcomas: A crucial pathway with many unknowns to exploit for therapy. J. Mol. Endocrinol. 2018, 61, T45–T60.
10. Mancarella, C.; Scotlandi, K. IGF2BP3 From Physiology to Cancer: Novel Discoveries, Unsolved Issues, and Future Perspectives. Front. Cell Dev. Biol. 2019, 7, 363.
11. Chen, B.; Li, J.; Chi, D.; Sahnoune, I.; Calin, S.; Girnita, L.; Calin, G.A. Non-Coding RNAs in IGF-1R Signaling Regulation: The Underlying Pathophysiological Link between Diabetes and Cancer. Cells 2019, 8, 1638.
12. Mancarella, C.; Morrione, A.; Scotlandi, K. Novel Regulators of the IGF System in Cancer. Biomolecules 2021, 11, 273.
13. Garofalo, C.; Mancarella, C.; Grilli, A.; Manara, M.C.; Astolfi, A.; Marino, M.T.; Conte, A.; Sigismund, S.; Care, A.; Belfiore, A.; et al. Identification of common and distinctive mechanisms of resistance to different anti-IGF-IR agents in Ewing's sarcoma. Mol. Endocrinol. 2012, 26, 1603–1616.
14. Sachdev, D.; Li, S.L.; Hartell, J.S.; Fujita-Yamaguchi, Y.; Miller, J.S.; Yee, D. A chimeric humanized single-chain antibody against the type I insulin-like growth factor (IGF) receptor renders breast cancer cells refractory to the mitogenic effects of IGF-I. Cancer Res. 2003, 63, 627–635.

15. Sachdev, D.; Singh, R.; Fujita-Yamaguchi, Y.; Yee, D. Down-regulation of insulin receptor by antibodies against the type I insulin-like growth factor receptor: Implications for anti-insulin-like growth factor therapy in breast cancer. Cancer Res. 2006, 66, 2391–2402.

16. Arteaga, C.L.; Kitten, L.J.; Coronado, E.B.; Jacobs, S.; Kull, F.C., Jr.; Allred, D.C.; Osborne, C.K. Blockade of the type I somatomedin receptor inhibits growth of human breast cancer cells in athymic mice. J. Clin. Investig. 1989, 84, 1418–1423.

17. Zhang, T.; Shen, H.; Dong, W.; Qu, X.; Liu, Q.; Du, J. Antitumor effects and molecular mechanisms of figitumumab, a humanized monoclonal antibody to IGF-1 receptor, in esophageal carcinoma. Sci. Rep. 2014, 4, 6855.

18. Huang, H.J.; Angelo, L.S.; Rodon, J.; Sun, M.; Kuenkele, K.P.; Parsons, H.A.; Trent, J.C.; Kurzrock, R. R1507, an anti-insulin-like growth factor-1 receptor (IGF-1R) antibody, and EWS/FLI-1 siRNA in Ewing's sarcoma: Convergence at the IGF/IGFR/Akt axis. PLoS ONE 2011, 6, e26060.

19. Shin, D.H.; Min, H.Y.; El-Naggar, A.K.; Lippman, S.M.; Glisson, B.; Lee, H.Y. Akt/mTOR counteract the antitumor activities of cixutumumab, an anti-insulin-like growth factor I receptor monoclonal antibody. Mol. Cancer Ther. 2011, 10, 2437–2448.

20. Leiphrakpam, P.D.; Agarwal, E.; Mathiesen, M.; Haferbier, K.L.; Brattain, M.G.; Chowdhury, S. In vivo analysis of insulin-like growth factor type 1 receptor humanized monoclonal antibody MK-0646 and small molecule kinase inhibitor OSI-906 in colorectal cancer. Oncol. Rep. 2014, 31, 87–94.

21. Beltran, P.J.; Calzone, F.J.; Mitchell, P.; Chung, Y.A.; Cajulis, E.; Moody, G.; Belmontes, B.; Li, C.M.; Vonderfecht, S.; Velculescu, V.E.; et al. Ganitumab (AMG 479) inhibits IGF-II-dependent ovarian cancer growth and potentiates platinum-based chemotherapy. Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res. 2014, 20, 2947–2958.

22. Wang, Y.; Lipari, P.; Wang, X.; Hailey, J.; Liang, L.; Ramos, R.; Liu, M.; Pachter, J.A.; Bishop, W.R.; Wang, Y. A fully human insulin-like growth factor-I receptor antibody SCH 717454 (Robatumumab) has antitumor activity as a single agent and in combination with cytotoxics in pediatric tumor xenografts. Mol. Cancer Ther. 2010, 9, 410–418.

23. Schmitz, S.; Kaminsky-Forrett, M.C.; Henry, S.; Zanetta, S.; Geoffrois, L.; Bompas, E.; Moxhon, A.; Mignion, L.; Guigay, J.; Knoops, L.; et al. Phase II study of figitumumab in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck: Clinical activity and molecular response (GORTEC 2008-02). Ann. Oncol. Off. J. Eur. Soc. Med. Oncol. 2012, 23, 2153–2161.

24. Pandini, G.; Wurch, T.; Akla, B.; Corvaia, N.; Belfiore, A.; Goetsch, L. Functional responses and in vivo anti-tumour activity of h7C10: A humanised monoclonal antibody with neutralising activity against the insulin-like growth factor-1 (IGF-1) receptor and insulin/IGF-1 hybrid receptors. Eur. J. Cancer 2007, 43, 1318–1327.

25. Buck, E.; Gokhale, P.C.; Koujak, S.; Brown, E.; Eyzaguirre, A.; Tao, N.; Rosenfeld-Franklin, M.; Lerner, L.; Chiu, M.I.; Wild, R.; et al. Compensatory insulin receptor (IR) activation on inhibition of insulin-like growth factor-1 receptor (IGF-1R): Rationale for cotargeting IGF-1R and IR in cancer. Mol. Cancer Ther. 2010, 9, 2652–2664.

26. Desbois-Mouthon, C.; Baron, A.; Blivet-Van Eggelpoel, M.J.; Fartoux, L.; Venot, C.; Bladt, F.; Housset, C.; Rosmorduc, O. Insulin-like growth factor-1 receptor inhibition induces a resistance mechanism via the epidermal growth factor receptor/HER3/AKT signaling pathway: Rational basis for cotargeting insulin-like growth factor-1 receptor and epidermal growth factor receptor in hepatocellular carcinoma. Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res. 2009, 15, 5445–5456.

27. Liu, R.; Tang, W.; Han, X.; Geng, R.; Wang, C.; Zhang, Z. Hepatocyte growth factor-induced mesenchymal-epithelial transition factor activation leads to insulin-like growth factor 1 receptor inhibitor unresponsiveness in gastric cancer cells. Oncol. Lett. 2018, 16, 5983–5991.

28. Solomon, V.R.; Alizadeh, E.; Bernhard, W.; Makhlouf, A.; Hartimath, S.V.; Hill, W.; El-Sayed, A.; Barreto, K.; Geyer, C.R.; Fonge, H. Development and preclinical evaluation of cixutumumab drug conjugates in a model of insulin growth factor receptor I (IGF-1R) positive cancer. Sci. Rep. 2020, 10, 18549.

29. Akla, B.; Broussas, M.; Loukili, N.; Robert, A.; Beau-Larvor, C.; Malissard, M.; Boute, N.; Champion, T.; Haeuw, J.F.; Beck, A.; et al. Efficacy of the Antibody-Drug Conjugate W0101 in Preclinical Models of IGF-1 Receptor Overexpressing Solid Tumors. Mol. Cancer Ther. 2020, 19, 168–177.

30. Favelyukis, S.; Till, J.H.; Hubbard, S.R.; Miller, W.T. Structure and autoregulation of the insulin-like growth factor 1 receptor kinase. Nat. Struct. Biol. 2001, 8, 1058–1063.

31. Mulvihill, M.J.; Cooke, A.; Rosenfeld-Franklin, M.; Buck, E.; Foreman, K.; Landfair, D.; O'Connor, M.; Pirritt, C.; Sun, Y.; Yao, Y.; et al. Discovery of OSI-906: A selective and orally efficacious dual inhibitor of the IGF-1 receptor and insulin receptor. Future Med. Chem. 2009, 1, 1153–1171.

32. Awasthi, N.; Zhang, C.; Ruan, W.; Schwarz, M.A.; Schwarz, R.E. BMS-754807, a small-molecule inhibitor of insulin-like growth factor-1 receptor/insulin receptor, enhances gemcitabine response in pancreatic cancer. Mol. Cancer Ther.

2012, 11, 2644–2653.

33. Carrasco-Garcia, E.; Martinez-Lacaci, I.; Mayor-Lopez, L.; Tristante, E.; Carballo-Santana, M.; Garcia-Morales, P.; Ventero Martin, M.P.; Fuentes-Baile, M.; Rodriguez-Lescure, A.; Saceda, M. PDGFR and IGF-1R Inhibitors Induce a G2/M Arrest and Subsequent Cell Death in Human Glioblastoma Cell Lines. Cells 2018, 7, 131.
34. George, B.; George, S.K.; Shi, W.; Haque, A.; Shi, P.; Eskandari, G.; Axelson, M.; Larsson, O.; Kaseb, A.O.; Amin, H.M. Dual inhibition of IGF-IR and ALK as an effective strategy to eradicate NPM-ALK(+) T-cell lymphoma. J. Hematol. Oncol. 2019, 12, 80.
35. Aiken, R.; Axelson, M.; Harmenberg, J.; Klockare, M.; Larsson, O.; Wassberg, C. Phase I clinical trial of AXL1717 for treatment of relapsed malignant astrocytomas: Analysis of dose and response. Oncotarget 2017, 8, 81501–81510.
36. Bergqvist, M.; Holgersson, G.; Bondarenko, I.; Grechanaya, E.; Maximovich, A.; Andor, G.; Klockare, M.; Thureson, M.; Jerling, M.; Harmenberg, J. Phase II randomized study of the IGF-1R pathway modulator AXL1717 compared to docetaxel in patients with previously treated, locally advanced or metastatic non-small cell lung cancer. Acta Oncol. 2017, 56, 441–447.
37. Gao, J.; Chesebrough, J.W.; Cartlidge, S.A.; Ricketts, S.A.; Incognito, L.; Veldman-Jones, M.; Blakey, D.C.; Tabrizi, M.; Jallal, B.; Trail, P.A.; et al. Dual IGF-I/II-neutralizing antibody MEDI-573 potently inhibits IGF signaling and tumor growth. Cancer Res. 2011, 71, 1029–1040.
38. Zhong, H.; Fazenbaker, C.; Chen, C.; Breen, S.; Huang, J.; Yao, X.; Ren, P.; Yao, Y.; Herbst, R.; Hollingsworth, R.E. Overproduction of IGF-2 drives a subset of colorectal cancer cells, which specifically respond to an anti-IGF therapeutic antibody and combination therapies. Oncogene 2017, 36, 797–806.
39. Haluska, P.; Menefee, M.; Plimack, E.R.; Rosenberg, J.; Northfelt, D.; LaVallee, T.; Shi, L.; Yu, X.Q.; Burke, P.; Huang, J.; et al. Phase I dose-escalation study of MEDI-573, a bispecific, antiligand monoclonal antibody against IGFI and IGFII, in patients with advanced solid tumors. Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res. 2014, 20, 4747–4757.
40. Chen, Y.M.; Qi, S.; Perrino, S.; Hashimoto, M.; Brodt, P. Targeting the IGF-Axis for Cancer Therapy: Development and Validation of an IGF-Trap as a Potential Drug. Cells 2020, 9, 1098.
41. Vaniotis, G.; Moffett, S.; Sulea, T.; Wang, N.; Elahi, S.M.; Lessard, E.; Baardsnes, J.; Perrino, S.; Durocher, Y.; Frystyk, J.; et al. Enhanced anti-metastatic bioactivity of an IGF-TRAP re-engineered to improve physicochemical properties. Sci. Rep. 2018, 8, 17361.
