**Stem Cells Implications in Neurocancerology**

**ABSTRACT**

Neural stem cell research holds great promise for regenerative medicine, tissue engineering, drug screening, and especially brain tumour therapies. Efficient strategies for brain glioblastoma therapies were established by the construction of vectors targeting oncoproteins or growth factors (i.e. IGF-I, AFP) present during the development of the embryonic and fetal nervous system tissues originating from neural stem cells. The neoplastic stem cells, PCC3 and PCC4, derived from mouse teratocarcinoma – tumor mimicking the structures of developing central nervous system - were transfected *in vitro* with the anti - gene IGF-I vectors (antisense and triple helix approaches). This strategy has completely stopped the synthesis of the IGF-I and converted the stem cells into immunogenic cells expressing MHC-I and B7, and inducing *in vivo* anti-tumour effect. The strategy of Anti IGF-I vaccines was applied with success for therapy of glioblastoma. The anti IGF-I strategy was recently combined with use of nanotechnology. Nanotechnology has played an important role in the advancement of stem cell and neuronal/glial cell investigations. The application of nanotechnology in stem cell research is based on the use of nanoparticles, NP, for targeted drug delivery. NP can also be used as delivery vehicles for therapeutics, especially targeted gene therapy. As an example, the NP (β-Cyclodextrin functionalized β-lactoglobulin or theranostic iron oxide) conjugated to IGF-I targeting related signal transduction pathway have created an anti-tumour effect leading to cancer cell apoptosis. Other studies have demonstrated that NP loaded with a chemotherapy drug and injected into mice with brain tumors, selectively targeted and killed cancer stem cells while sparing normal cells.

**Keywords:** stem cells, IGF-I, nervous system development, neoplasia, self-regeneration,

nanotechnology, therapeutic

1. **INTRODUCTION**

Stem cell research holds great promise for regenerative medicine, tissue engineering, drug screening and clinical therapies. Stem cells are related to the phenomenon of neurogenesis [1,2]. Neurogenesis takes place when neural stem cells (NSC) generate new multipotent cells. In neurogenesis immature NSC exist in the central nervous system, CNS, in hippocampus and ventricles; they undergo differentiation and settle in the brain site where they activate a process of synaptogenesis [3,4]. The NSC generate new functional neurons and glia [5]. This process begins during foetal development and persists in adult life [5,6]. Neurogenesis is affected by different physiologic aspects associated with increased production of brain-derived neurotrophic factor (BDNF) and expression of genes necessary for proliferation and differentiation of NSC [7]. Development of NSC is mediated by insulin-like growth factor 1 and its receptor (IGF-1R); considering that is the convergence between an embryonic and tumor development, the IGF-I and its receptor was proposed as a target to treat the progression of the glioblastoma tumor [8,9]. The objective of this review is to describe the NSC in adults, as well as a relationship between IGF-I, IGF-1R and NSC implied during postnatal life development. Moreover, the use of IGF-I as a target brain tumour glioblastoma immuno-gene therapy modified by use of nanotechnology will be also considered. Nanotechnology provides a way to achieve precise control over stem cell differentiating into neuroglial cells behavior by manipulating their microenvironment at the nanoscale [10,11] Considering glioblastoma - the most common primary brain tumour in adults, with a prognosis for survivals below 1 year, the solution for an efficient therapy constitutes the permanent challenge [9].

**2. NEURAL STEM CELLS**

In the 1980-90s, the advances in electron microscopy and molecular biology have demonstrated the existence of totipotent stem cells (NSC), their multiplication in CNS during differentiation process and moreover the relation existing between their differentiation process and the growth factors responsible for neuronal maturation, self-regeneration, synaptogenesis, and cerebral plasticity [12]. The stem cells giving rise to synaptogenesis are involved also in their role played in the processus of learning and memory [13].

The stem cells of adult CNS can produce new neurons and cells of the glia: the embryogenic stem cells, isolated in human embryos of only 100 cells, can generate any type of cells of the body These stem cells can be cultured, multiplied and then transplanted into the Central Nervous System of an adult animal. They survive successfully in the hippocampus and olfactory bulbs and differentiate into mature neurons [2,5,14].

As far as history of nervous system description is considered, Santiago Ramon y Cajal described first the central nervous system (CNS) and neurons in details. In 1965 Altman evidenced that in adult rat’s hippocampus exist neurogenesis in the granule cells zone (SGZ) of the dentate gyrus [15], and also in the ventricular subventricular zone (V-SVZ) of the lateral ventricles [15-17]. As to the role of the dentate gyrus (DG) composed by different layers, one of them is the sub granulate zone (SBZ) where the NSC are concentrated. Different factors influence neurogenesis, that leads NSCs present in the DG and SBZ to astrogliosis, neurogliosis and vascular remodelling [14,18].

In 1978/79 Trojan and Uriel using a marker of alpha-fetoprotein (AFP) and a model of rat brain, the detailed CNS development was described for the first time coming from embryonic neurogenesis up to differentiated neuron and glial cells; AFP was absent from either undifferentiated or fully differentiated cells [19]. The localization of AFP and its mRNAs was investigated in parallel in the teratocarcinomas presenting similar structures (reproducing the structures of brain development). AFP-mRNA was observed only in differentiating struc­tures. The analysed structures of neuro/glial neoplastic development in teratocarcinoma, from stem cells to glial differentiation, portrayed a glioma-like tumour. Studies using mammalian CNS models and teratocarcinoma models have shown the presence of AFP in both glial and neuronal cells [20,21]. On the contrary using another biomarker, the neoplastic growth factor, Insulin-like growth factor I, IGF-I [22] the presence of IGF-I was demonstrated only in glial cells being absent in neuroblastic cells [23]. IGF-I is considered as the most important growth factor of normal and neoplastic development, including CNS [24]. IGF-I is a polypeptide of 70-amino-acid playing a role in normal NSCs by inducing differentiation, proliferation or survival of neurons in SVZ and DG [25,26] .

There are different mechanisms explaining neurogenesis and human cognitive functions preventing the death of new neurons or their relation with angiogenesis [27]. Among different factors affecting neurogenesis the immunologic factors play an important role in development of NSC and neurogenesis during adult life, especially cytokines like interleukin-1 (IL-1) [28], tumour necrosis factor alpha (TNF-α) [29] or interleukin-6(IL-6) [30]. Related to immune mechanism IGF-I activates genes like RIT-1 to produce Ras-related GTPase and increase proliferation of hippocampal NSCs [31]. Besides that, it helps a maturation process of transformation NSCs into neurons, which are integrated in dendritic trees [32].

The totipotent stem cells are conducting to auto-regeneration of CNS [33-36]. Stem cells are periodically divided into 2 main areas: the ventricles which contain the spinal brain fluid (CSF) and the hippocampus. In the adult brain, newborn neurons have been found in the hippocampus and in the olfactory bulb [2,37]. Then the differentiating neurons are principally involved in the following physiologic processes: The BDNF keeps neurons alive; the ciliary neurotropic factor (CNTF) protects neurons from death; neurotropin-3 (NT-3) promotes the formation of oligodendrocytes; EGF, an inducer of the division of brain stem cells, and FGF, in low doses keep alive several types of cells; IGF-I stimulates the birth of neurons and glia cells [2,5,14,26,27,37].

**3. STEM CELLS, CANCEROGENESIS AND THERAPEUTIC**

The comparison of two models, developing rat CNS and murine teratocarcinoma reproducing the CNS development (both models coming from embryonic stem cells up to fetal neuroglial cells) showed that there is a convergence between embryonic / fetal development and neoplastic development [19,20,38,39]. The results were obtained using AFP marker. The AFP was present not only in glial but also in neuronal cells of differentiation, which has limited its usefulness for differentiational diagnosis and therapy of glial and neuronal derivatived tumors. A new oncoprotein IGF-I, presented only in glial cells of normal or neoplastic development but absent in neuronal cells, was considered for therapeutic purpose [22,23,40]. Logically, to stop the neoplastic development, the arrest of the synthesis of IGF-I in cancer cells of glioblastoma, in the "source" at the level of transcription or translation was considered, using the technologies of antisense created by group F. Jacob and Weintraub [41,42] or triple helix created by groups of P. Dervan and of C. Helene [43,44].

The translation level of IGF-I was targeted in PCC4 stem cells of teratocarcinoma and in C6 rat glioma malignant cells by antisense approach using a vector expressing antisense IGF-I RNA [23]. This strategy has given historically the birth of a new oncology domain - cancer gene therapy (immuno-gene therapy) [45]. This technology, as well using antisense as triple helix approaches, has yielded positive results *in vitro,* stopping the synthesis of IGF-I in both cell cultures, and *in vivo*, inducing an antitumor immune response mediated by TCD8 + cells, and then stopping the neoplastic development of the tumors [21,46-48] (Figures 1 – 5).

The proposed mechanism of anti – gene (antisense or triple helix) therapy concerns the growth factors and their receptors (IGF-I, TGF-beta, EGF, IGF-I-R, EGF-R) – a combination of an increased anti-tumor immune response (CD8 +), and an inhibition of the transduction pathway of the PI3K / AKT / GWK3 / GS signal that is involved in the transformed phenotype of glioma and teratocarcinoma [40,49,50]. New or proposed therapies of glioblastoma are based either on immune treatment or on immuno-gene strategies, including inhibitors, and the anti – gene strategy The last approach, anti IGF-I combined with phytochemical and nanotechnology has now been introduced into clinical trials (the median survival of patients has reached 2 years, and in some cases 3 or 4 years) [9,51,52]. Other AS approaches targeting TGF-beta or VEGF, their receptors and their downstream transduction signalling elements appear to offer hope for a promising solution [53,54].



**Figure 1.** Teratocarcinoma structures resulted of injection into 129 mice of stem cells – PCC3 embryonal carcinoma cells. (left) Neuroepithelial rosette surrounded by neuroepithelial cells, HE, x250; (middle) Higher magnification of the same poorly differentiated neuroepithelial rosette, x400. (right) More advanced step of neuroepithelial differentiation showing a cyst of nervous origin ‘’pathological neural tube’’. The wall of the cyst as well its neighborhood is constituted by the same type of neuroepithelial cells. Neuroepithelila cells surrounding the cyst present a character of neurospongium, HE, x250



**Figure 2.** Teratocarcinoma resulted of injection of stem cells, PCC3 cells, showing an intermediate step of cyst differentiation (bottom down) if compared to two structures presented in figure 1. The differentiating neuroependymal tube and groups of cells arranged in clusters (arrow) are labelled with antibodies anti AFP, Immunoperoxidase, x250

  **IGF-I Antisense IGF-I Triple helix**

 Arrest of translation Arrest of transcription

 IGF RNA IGF RNA IGF DNA IGF RNA

 (antisense RNA Sense mRNA Sense Antisense (23 pb RNA

 transcribed by vector) transcribed by vector)

 3’ 5’ 5’ 3’ poly A

 I I I :: I I

 I I IGF-I protein I :: I I

 I I I :: I I

 3’ 5’ 5’ 3’ cap 5’

 5’ :: 3’ 5’ 3’ poly A

 I :: I I :: I # I

 I :: I I :: I # I

 I :: I I :: I # I

 5’ :: 3’ 5’ 3’# cap 5’

 No protein No protein

 **Figure 3.** Schema of Antisense and Triple helix technology to arrest Growth Factor, GF.

 In antisense technology the end result is the inhibition of GF mRNA (sense RNA) activity by

 binding to the antisense RNA. In GF triple helix technology the oligopurine third strand (23

 bp) forms RNA-DNA triple helix with GF gene.

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 **Tumour cells *in vitro***

 IGF-I (+), expression of IGF-I mRNA and IGF-I (TK) receptor

 Transfection Vector IGF-I antisens

 **Tumor transfected cells** *in vitro*

 IGF-I (-), expression of IGF-I antisens RNA and IGF-I (TK) receptor

 (TK) PI3K / AKT / GSK3 / GS

 cAMP Bcl 2

 TAP 1,2 PKC

 MHC-I B7 apoptotic cells

Figure 4. Mechanism of immunogene therapy. After transfection *in vitro* of stem cells - PCC3 embryonal carcinoma cells, using Antisens IGF-I vector, the cells stop to synthesize IGF-I, and become immunogenic, expressing MHC-I and B7 antigens. One part of cells enter in apoptosis Celulas “antisentido” (anti IGF-I). The injection of these transfected cells into animal induce anti tumor immune response mediated by CD8 lymphocytes]. Abreviaturas: TAP 1,2 (transporter associated with antigen processing antigen); TK (tyrosine kinase); PI3K (phosphatidyinositol 3 kinase); PDK1 (phosphoinositide-dependent kinase 1); AKT (PKB, protein kinase B); Bcl 2 (key molecule of apoptose); GSK3 (glycogene synthetase kinase 3); GS (glycogene synthetase); PKC (protein kinase C).



**Figure 5.** Tumor regression induced by injection of antisense IGF-I expressing PCC3 transfected stem cells. (left) Teratocarcinoma 4 days following transfected PCC3 cells injection, showing embryonal carcinoma cells (open arrow), neuroblastic cells arranged in pseudorosettes (star), and nervous-system derived cells scattered about blood vessel (broken arrow), HE, x110. (middle) Serial section stained with anti CD8 antibodies, x110. (right) Teratocarcinoma 9 days following transfected cell injection, showing embryonal carcinoma cells and pseudorosettes of neuroblastic cells (star), and disentegrating and necrotic tissue (black circle), HE, x110.

**4. NEW HORIZONS: STEM CELLS AND NANOTECHNOLOGY**

Nanotechnology has played an important role in the advancement of stem cell and neuronal/glial cell research as follows [10,55-58]:

The unique properties of nanomaterials, including their small size, high surface area, and tunable physicochemical properties, have enabled researchers to manipulate and control cellular behavior with a high degree of precision. Nanotechnology offers unique opportunities to address this challenge by providing precise control of cell behavior through manipulation of the cellular microenvironment. However, traditional methods of controlling the microenvironment lack the precision required for successful and reproducible differentiation. Nanotechnology provides a way to achieve precise control over stem cell behavior by manipulating their microenvironment at the nanoscale. Similarly, neurons and glial cells require specific microenvironments for growth and differentiation and nanotechnology can be used to create scaffolds that support their growth and distinction. In addition to scaffolds, nanoparticles have also been used to deliver therapeutic agents directly to stem cells or the tissues they are intended to regenerate.

In particular, nanomaterials have been developed to mimic the extracellular matrix (ECM) and provide physical and chemical cues to guide stem cell behavior. Additionally, nanoparticles can act as delivery vehicles for therapeutics or genetic material, enabling targeted gene therapy and drug delivery. Furthermore, one of the major applications of nanotechnology in stem cell research is the development of nanoscale scaffolds that mimic the ECM found in the tissues. Nanotechnology has been used to create scaffolds that support the growth and differentiation of neurons and glial cells, with potential applications in the treatment of neurodegenerative diseases and spinal cord injuries. These scaffolds can be designed to provide physical support, as well as chemical and mechanical cues to guide stem cell differentiation and tissue regeneration.

Concerning nanomaterials for stem cell research, one example is graphene, a two-dimensional material composed of carbon atoms arranged in a hexagonal lattice. Graphene's unique properties, including its high surface area, mechanical strength, and electrical conductivity, make it an attractive material for creating scaffolds for tissue engineering applications. Researchers have demonstrated that graphene-based scaffolds can support the growth and differentiation of various types of stem cells, including neural stem cells. In one study, it was demonstrated that graphene oxide nanosheets increased the adhesion and proliferation of neural progenitor cells.

Another application of nanotechnology in stem cell research is the use of nanoparticles for targeted drug delivery. Nanomaterials can also be used as delivery vehicles for therapeutics or genetic material, enabling targeted gene therapy and drug delivery. They can be engineered to release drugs or other therapeutic agents in response to specific stimuli, such as changes in pH or temperature. In one study, researchers developed gold nanoparticles functionalized with a protein that targets cancer stem cells. When these nanoparticles were loaded with a chemotherapy drug and injected into mice with brain tumors, they selectively targeted and killed cancer stem cells while sparing normal cells. Overall, the use of nanotechnology in stem cell and neuronal/glial cell research holds great promise for regenerative medicine, tissue engineering, and drug screening. The integration of nanotechnology with stem cell and neuronal/glial cell research has the potential to revolutionize the field of regenerative and therapeutic medicine and neuroscience.

The insights gained from studying brain tumoral development coming from cancer stem cells, in relation with tumoral therapies translate into innovative nanotechnology-driven therapies: **a) Drug delivery systems**: Nanocarriers bypass the blood-brain barrier to deliver targeted therapies, such as chemotherapeutics or RNA-based treatments, to tumour sites [59,60-62]; **b) Gene editing:** CRISPR-Cas9 systems, delivered via nanoparticles, target oncogenes while offering insights into gene functions critical for brain evolution [63]; **c) Immunotherapy**: Nanoparticles, NP, present tumor antigens to the immune system, enhancing responses against glioblastoma. The immunotherapy using nanotechnology constitutes currently the promising approach in cancer treatment [52,60-70]; NP related therapy recently approved for GBM treatment is NanoThermTM [11] and is based on iron oxide nanoparticles and the thermal ablation of the tumor with a magnetic field. Ongoing cancer immune and gene therapy studies involve nanotechnology mechanisms related to signal transduction pathways as well as immune response [66,67,71-73]. Future research should focus on refining nanocarriers for personalized and adaptive therapies, particularly immunotherapies [60,66,69,70,74]

**List of Abbreviations**

GBM, *glioblastoma multiforme*; NSC, neural stem cells; CNS, central nervous system; IGF-I, Insulin-like growth factor 1;IGF-I-R, receptor of IGF-I; EGF,Epidermal growth factor*;* VEGF, vascular endothelial growth factor*;* TGF-beta, Transforming growth factor beta; HGF, hepatocyte growth factor; PDGF, platelet-derived growth factor; CD8 T, lymphocytes expressing CD8; TMZ, temozolomide; DCs, dendritic cells; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; AFP, alpha-fetoprotein; AS, antisense; TH, Triple -helix; pMT*,* plasmid containing promotor of metallothionein; TAP-1 and -2 antigens, transporter associated with antigen processing; TK, tyrosine kinase; PI3K, phosphatidyinositol 3 kinase; PDK1 phosphoinositide-dependent kinase 1; Bcl 2, key molecule of apoptose; GSK3, glycogene synthetase kinase 3; GS, glycogene synthetase; PKC, protein kinase C; DCs, dendritic cells;; ACT, [Adoptive T cell-receptor therapy;](https://www.bing.com/ck/a?!&&p=cf92b68f56492baaJmltdHM9MTcwMzg5NDQwMCZpZ3VpZD0zM2Y0ODU3YS01OGIwLTZmNzQtMTg4ZC05NjhkNTkwMjZlMDcmaW5zaWQ9NTcyMA&ptn=3&ver=2&hsh=3&fclid=33f4857a-58b0-6f74-188d-968d59026e07&u=a1aHR0cHM6Ly93d3cuZnJvbnRpZXJzaW4ub3JnL2FydGljbGVzLzEwLjMzODkvZmltbXUuMjAyMC4wMDE3Ni9mdWxs&ntb=1) AFP, alpha-fetoprotein; AS, antisens; TH, Triple-helix; pMT*,* plasmid containing promotor of metallothionein; TAP-1 and -2 antigens, transporter associated with antigen processing; BDNF, brain derived neurotrophic factor; NP, Nanoparticles; CNTs, Carbon nanotubes; SGZ, granule cells zone; DG, dental gyrus; V-SVZ, ventricular subventricular zone; SBZ, sub granulate zone; IL-1, interleukin 1; TNF alpha, tumour necrosis factor alpha; CSF, spinal brain fluid; OB, olfactory bulb; CNTF,ciliary neurotropic factor; NT-3, neurotropin-3.

**Ethics Approval**

Not applicable.

**REFERENCES**

1. Ming G-L, Song H. Adult neurogenesis in the mammalian brain: Significant answers and significant questions. Neuron. 2011:70(4):687-702. doi: 10.1016/j.neuron.2011.05.001
2. Gage FH, Temple S. Neuron perspective neural stem cells: Generating and regenerating the brain. Neuron. 2013;80(3):588-601. doi: [10.1016/j.neuron.2013.10.037](https://doi.org/10.1016/j.neuron.2013.10.037)
3. [Hsu YC](http://www.ncbi.nlm.nih.gov/pubmed?term=%22Hsu%20YC%22%5BAuthor%5D), [Fuchs E](http://www.ncbi.nlm.nih.gov/pubmed?term=%22Fuchs%20E%22%5BAuthor%5D). (2012) A family business: stem cell progeny join the niche to regulate homeostasis. Nat Rev Mol Cell Biol. 2012;13(2):103-114. doi: 10.1038/nrm3272.
4. [Nguyen LV](http://www.ncbi.nlm.nih.gov/pubmed?term=%22Nguyen%20LV%22%5BAuthor%5D), [Vanner R](http://www.ncbi.nlm.nih.gov/pubmed?term=%22Vanner%20R%22%5BAuthor%5D), [Dirks P](http://www.ncbi.nlm.nih.gov/pubmed?term=%22Dirks%20P%22%5BAuthor%5D), [Eaves CJ](http://www.ncbi.nlm.nih.gov/pubmed?term=%22Eaves%20CJ%22%5BAuthor%5D). Cancer stem cells: an evolving concept. Nat Rev Cancer. 2012;12(2):133-143. doi: 10.1038/nrc3184.
5. Pino A, Fumagalli G, Bifari F, Decimo I. New neurons in adult brain: distribution, molecular mechanisms and therapies. Biochem Pharmacol. 2017;141:4–22. doi: 10.1016/J.BCP.2017.07.003
6. Gebara E, Bonaguidi MA, Beckervordersandforth R, Sultan S, Udry F, Gijs P-J, et al. Heterogeneity of radial glia-like cells in the adult hippocampus. Stem Cells. 2016; 34: 997--1010.  [doi](https://doi): [10.1002/stem.2266](https://doi.org/10.1002/stem.2266)
7. Phillips C. Brain-derived neurotrophic factor, depression, and physical activity: Making the neuroplastic connection. Neural Plast. 2017;1:1–17. doi: [10.1155/2017/7260130](https://doi.org/10.1155/2017/7260130)
8. Schlenska-Lange A, Knüpfer H, Lange TJ, Kiess W, Knüpfer M. Cell proliferation and migration in glioblastoma multiforme cell lines are influenced by insulin-like growth factor I in vitro. Anticancer Res. 2017;28(2A):1055–1060. PMID: 18507054.
9. Trojan A, Lone YC, Briceno I, Trojan J. Anti – Gene IGF-I vaccines in cancer gene therapy: Case of glioblastoma. Review. Curr Med Chem. 2024;31(15):1983-2002.
10. Khan FA, Almohazey D, Alomari M, Almofty SA. Impact of nanoparticles on neuron biology: current research trends. Int J Nanomed. 2018;13:2767-2776. doi: [10.2147/IJN.S165675](https://doi.org/10.2147/ijn.s165675)
11. [Grzegorzewski](https://pubmed.ncbi.nlm.nih.gov/?term=Grzegorzewski+J&cauthor_id=40076445) J, [Michalak](https://pubmed.ncbi.nlm.nih.gov/?term=Michalak+M&cauthor_id=40076445) M,  [Wołoszczuk](https://pubmed.ncbi.nlm.nih.gov/?term=Wo%C5%82oszczuk+M&cauthor_id=40076445) M,  [Bulicz](https://pubmed.ncbi.nlm.nih.gov/?term=Bulicz+M&cauthor_id=40076445) M, [Majchrzak-Celińska](https://pubmed.ncbi.nlm.nih.gov/?term=Majchrzak-Celi%C5%84ska+A&cauthor_id=40076445) A. Nanotherapy of glioblastoma - where hope grows. Int J Mol Sci. 2025;26(5):1814. [doi: 10.3390/ijms26051814](https://doi.org/10.3390/ijms26051814)
12. [Castrén M](http://www.ncbi.nlm.nih.gov/pubmed?term=%22Castr%C3%A9n%20M%22%5BAuthor%5D). (2012) Neural stem cells. Results Probl Cell Differ. 2012;54:33-40. doi: 10.1007/978-3-642-21649-7\_3
13. Vivar C, Peterson BD, van Praag H. Running revires the neuronal network of adult-born dentate granule cells. Neuroimage.2016;131:29-41. doi: [10.1016/j.neuroimage.2015.11.031](https://doi.org/10.1016/j.neuroimage.2015.11.031)
14. Song J, Olsen RHJ, Sun J, Ming G-L, Song H. Neuronal circuitry mechanisms regulating adult mammalian neurogenesis. Cold Spring Harb Perspect Biol. 2016*;*8(8): a018937. doi: 10.1101/cshperspect.a018937.
15. Altman J, Das GD. Autoradiographic and histological evidence of postnatal hippocampal neurogenesis in rats. J Comp Neurol. 1965;124(3):319–335. [doi](http://doi): 10.1002/cne.901240303
16. Rushing G, Ihrie RA. Neural stem cell heterogeneity through time and space in the ventricular-subventricular zone. Front Biol. 2016;11(4):261–284. doi: [10.1007/s11515-016-1407-1](https://doi.org/10.1007/s11515-016-1407-1)
17. Zhao H, Alam A, San C-Y, Eguchi S, Chen Q, Lian Q, et al. Molecular mechanisms of brain-derived neurotrophic factor in neuro- protection: Recent developments. Brain Res.2017;1665 :1–21. doi: [10.1016/j.brainres.2017.03.029](https://doi.org/10.1016/j.brainres.2017.03.029)
18. Lugert S, Basak O, Knuckles P, Haussler U, Fabel K, Goetz M, et al. Cell Stem Cell article quiescent and active hippocampal Neural Stem Cells with distinct morphologies respond selectively to physiological and pathological stimuli and aging. Stem Cell. 2017;6:445–456. doi: [10.1016/j.stem.2010.03.017](file:///C%3A%5CUsers%5Cgenet%5CDocuments%5C10.1016%5Cj.stem.2010.03.017)
19. Trojan J, Uriel J. Intracellular localisation of alphafeprotein and serum albumin in the central nervous system of the rat during foetal and post-natal development. CR Acad Sci. 1979; 289(15):1157-1160. (In French) PMID: 95002
20. Trojan J, Uriel J, Deugnier MA, Gaillard J. Immunocytochemical quantitative study of alphafetoprotein in normal and neoplastic neural development. Dev Neurosci 1984; 6; 251-9. doi: [10.1159/000112352](https://doi.org/10.1159/000112352)
21. Trojan J, Naval J, Johnson T, Lafarge-Frayssinet C, Hajeri-Germond M, Farges O*,* et al. Expression of serum albumin and of alphafetoprotein in murine normal and neoplastic primitive embryonic structures of teratocarcinoma. Mol Reproduct Dev. 1995;42(4):369-378. [doi: 10.1002/mrd.1080420402](%20https%3A//doi.org/10.1002/mrd.1080420402)
22. Kiess, W,  [Lee](https://pubmed.ncbi.nlm.nih.gov/?term=Lee+L&cauthor_id=2538309) L, [Graham](https://pubmed.ncbi.nlm.nih.gov/?term=Graham+DE&cauthor_id=2538309) DE, [Greenstein](https://pubmed.ncbi.nlm.nih.gov/?term=Greenstein+L&cauthor_id=2538309) L, [Tseng](https://pubmed.ncbi.nlm.nih.gov/?term=Tseng+LY&cauthor_id=2538309) LY,  [Rechler](https://pubmed.ncbi.nlm.nih.gov/?term=Rechler+MM&cauthor_id=2538309) MM, et al. Rat C6 glial cells synthesize insulin-like growth factor I (IGF-I) and express IGF-I receptors and IGF-II/mannose 6-phosphate receptors. Endocrinol. 1989;124(4):1727–1736. doi: [10.1210/endo-124-4-1727](https://doi.org/10.1210/endo-124-4-1727)
23. Trojan J, Blossey BK, Johnson T, Rudin S, Tykocinski M, Ilan J, et al. Loss of tumorogenicity of rat glioblastoma directed by episome-based antisense cDNA transcription of insulin-like growth factor I. Proc Natl Acad Sci USA. 1992;189(11):4874-4878. doi: [10.1073/pnas.89.11.4874](https://doi.org/10.1073/pnas.89.11.4874)
24. Pollak MN, Schernhammer ES, Hankinson SE. Insulin-like growth factors and neoplasia. Nature Rev Cancer. 2004;4: 505–518. doi: [10.1038/nrc1387](https://doi.org/10.1038/nrc1387)
25. Ziegler AN, Levison SW, Wood TL. Insulin and IGF receptor signalling in neural-stem-cell homeostasis. Nat Rev Endocrinol. 2014;11(3):161–170. doi: [10.1038/nrendo.2014.208](file:///C%3A%5CUsers%5Cgenet%5CDocuments%5CDocuments%5C%21%21%21%20BP%20Int%20-%20Stem%20cells%5C10.1038%5Cnrendo.2014.208)
26. Yuan H, Chen R, Wu L, Chen Q, Hu A, Zhang T, et al. The regulatory mechanism of neurogenesis by IGF-1 in adult mice. Mol Neurobiol. 2015;51(2):512–522. doi: [10.1007/s12035-014-8717-6](https://doi.org/10.1007/s12035-014-8717-6)
27. Mastrorilli V, Scopa C, Saraulli D, Costanzi M, Scardigli R, Rouault, JP, et al. Physical exercise rescues defective neural stem cells and neurogenesis in the adult subventricular zone of Btg1 knockout mice. Brain Struct Funct. 2017;222(6):2855–2876. doi: 1[0.1007/s00429-017-1376-4](file:///C%3A%5CUsers%5Cgenet%5CDocuments%5CDocuments%5C%21%21%21%20BP%20Int%20-%20Stem%20cells%5C0.1007%5Cs00429-017-1376-4)
28. Goshen I, Kreisel T, Ounallah-Saad H, Renbaum P, Zalzstein Y, Ben-Hur T, et al. A dual role for interleukin-1 in hippocampal-dependent memory processes. Psychoneuroendocrinol. 2017;32(8–10):1106–1115. doi: [10.1016/j.psyneuen.2007.09.004](https://doi.org/10.1016/j.psyneuen.2007.09.004)
29. Zhiguo Chen1, Theo D. Palmer. Differential roles of TNFR1 and TNFR2 signaling in adult hippocampal neurogenesis. Brain Behav Immun. 2013;30:45–43. doi: [10.1016/j.bbi.2013.01.083](https://doi.org/10.1016/j.bbi.2013.01.083)
30. Heese K. Functional repertoire of interleukin-6 in the central nervous system – a review. Restor Neurol Neurosci. 2017;35(6):693–701. doi:10.3233/RNN-170772
31. Mir S, Cai W, Carlson SW, Saatman KE, Andres DA. IGF-1 mediated neurogenesis involves a novel RIT1/Akt/Sox2 cascade. Sci Rep. 2017;7(1): 3283. doi: [10.1038/s41598-017-03641-9](file:///C%3A%5CUsers%5Cgenet%5CDocuments%5CDocuments%5C%21%21%21%20BP%20Int%20-%20Stem%20cells%5C10.1038%5Cs41598-017-03641-9)
32. Nieto-Estévez V, Oueslati-Morales CO, Li L, Pickel J, Morales AV, Vicario-Abejon C. Brain Insulin-Like Growth Factor-I directs the transition from Stem Cells to mature neurons during postnatal/adult hippocampal neurogenesis. Stem Cells. 2016;34(8): 2194–2209.  [doi](http://doi): 10.1002/stem.2397
33. Miyajima A, Tanaka M, Itoh T. [Stem/progenitor cells in liver development, homeostasis, regeneration, and reprogramming.](https://pubmed.ncbi.nlm.nih.gov/24792114/)  Stem Cell. 2014;14(5):561-574. doi: 10.1016/j.stem.2014.04.
34. Dulak J, Szade K, Szade A, Nowak W, Józkowicz A. [Adult stem cells: hopes and hypes of regenerative medicine.](https://pubmed.ncbi.nlm.nih.gov/26200199/)  Acta Biochim Pol. 2015;62(3):329-37. doi: 10.18388/abp.2015\_1023.
35. Laplane L, Solary E. Towards a classification of stem cells Elife. 2019;8:e46563. doi: 10.7554/eLife.46563.
36. Tian Z, Yu T, Liu J, Wang T, Higuchi A. [Introduction to stem cells.](https://pubmed.ncbi.nlm.nih.gov/37678976/)  Prog Mol Biol Transl Sci. 2023;199:3-32. doi: 10.1016/bs.pmbts.2023.02.012.
37. Toda T, Gage FH. Review: adult neurogenesis contributes to hippocampal plasticity. Cell Tissue Res*.* 2018;373(3):693-709. doi: 10.1007/s00441-017-2735-4.
38. Weatherbee BAT, Cui T, Zernicka-Goetz M. [Modeling human embryo development with embryonic and extra-embryonic stem cells.](https://pubmed.ncbi.nlm.nih.gov/33333069/)  Dev Biol. 2021;474:91-99. doi: 10.1016/j.ydbio.2020.12.010.
39. Ferrai C, Schulte C. [Mechanotransduction in stem cells.](https://pubmed.ncbi.nlm.nih.gov/38729084/)  Eur J Cell Biol. 2024;103(2):151417. doi: 10.1016/j.ejcb.2024.151417
40. Trojan J. Establishment of cancer gene therapy. Cambridge Scholars Publishing: UK, 2023. ISBN-13: 978-1-5275-9389-3
41. Rubenstein JL, Nicolas JF, Jacob F. Nonsense RNA: a tool for specifically inhibiting the expression of a gene in vivo. C R Acad Sci Paris III. 1984;299: 271-274. doi: 10.1090/S0002-9947-1952-0051341-6
42. Weintraub H, Izant J, Harland R. Antisense RNA as a molecular tool for genetic analysis. Trends Genetics.1985*;*1(1): 23-25. doi: 10.1016/S0168-9525
43. Dervan P. Reagents for the site‑specific cleavage of megabase DNA. Nature. 1992;359:87- 88. [doi : 10.1038/359087a0](http://dx.doi.org/10.1038/359087a0)
44. Hélène C. Control of oncogene expression by antisense nucleic acid. Eur J Cancer. 1994;30A:1721-1726. [doi : 10.1016/j.ejca.1994](http://dx.doi.org/10.1016/j.ejca.1994)
45. Trojan J, Johnson T, Rudin S, Ilan Ju, Tykocinski M, Ilan J. Treatmenand prevention of rat glioblastoma by immugenic C6 cells expressing antisense insulin-like growth factor I RNA. Science. 1993;259:94-97. [doi: 10.1126/science.8418502](https://doi.org/10.1126/science.8418502)
46. Trojan J, Johnson T, Rudin S, Blossey B., Kelley, Shevelev A, et al. Gene therapy of murine teratocarcinoma: separate functions for insulin-likegrowth factors I and II in immunogenicity and differentiation. Proc Natl Acad Sci USA. 1994;91: 6088-6092. doi: 10.1073/pnas.93.7.2909
47. Ly A, François JC, Upegui-Gonzalez LC, Swiercz B, Bedel C, Duc HT, et al. Alteration in tumorigenicity of embryonal carcinoma cells by IGF-I triple-helix induced changes in immunogenicity and apoptosis. Life Sci. 2001;68(3): 307-319. doi: [10.1016/s0024-3205(00)00936-x](https://doi.org/10.1016/s0024-3205%2800%2900936-x)
48. Quintero G, Guzman A, Gomez D, Kasparzk H, Penagos P, Siachoque H, et al.  **Glioblastoma - application of gene therapy during a quarter of a century: Anti - Gene IGF-I strategy.** Acta Scientifc Cancer Biology. 2020;4(1):38-45. [doi: 10.31080/ASCB.2020.04](https://doi.org/10.31080/ASCB.2020.04)
49. Castillo T, Trojan A, Noguera MC, Jay ML, Crane C, Alvarez A, et al. Epistemiologic experience in elaboration of molecular biology technology for immunogene therapy (in Spanish). Rev Cien. 2016; 2(25):228-240. doi: 10.14483/udistrital.jour.RC.2016.25.a6.
50. Dmitrenko VV, Kavsan VM, Boyko OI, Rymar VI, Stepanenko AA, Balynska OV, et al. Expression of genes belonging to the IGF-system in glial tumors. Tsitol Genet. 2017;45(5): 41–57. PMID: 22168049
51. Hernandez-Ramos R-M, Castillo-Maldonado I,  Rivera-Guillén M-A, Ramírez-Moreno A, Serrano-Gallardo L-B, Pedroza-Escobar D. [Plant phenolics and lectins as vaccine adjuvants.](https://pubmed.ncbi.nlm.nih.gov/31333121/)  Curr Pharm Biotech 2019; 20(15): 1236-43. doi: [10.2174/1389201020666190716110705](https://doi.org/10.2174/1389201020666190716110705)
52. Ram Kumar Pandian S, Rencilin CF, Sundar K. Emerging nanomaterials for cancer immunotherapy. Explor Med 2021;2:208-231. doi: 10.37349/emed.2021.0004.
53. Nadal R, [Amin](https://pubmed.ncbi.nlm.nih.gov/?term=Amin+A&cauthor_id=27059553) A, [Geynisman](https://pubmed.ncbi.nlm.nih.gov/?term=Geynisman+DM&cauthor_id=27059553) DM, Voss MH, Weinstock M, Doyle J, et al.[Safety and clinical activity of vascular endothelial growth factor receptor (VEGFR)-tyrosine kinase inhibitors after programmed cell death - inhibitor treatment in patients with metastatic clear cell renal cell carcinoma.](https://pubmed.ncbi.nlm.nih.gov/27059553/?from_term=vascular+endothelial+growth+factor+receptor+and+therapy&from_pos=10) Ann Oncol. 2016;27(7):1304-1311. doi: [10.1093/annonc/mdw160](https://doi.org/10.1093/annonc/mdw160)
54. Hau P, Jachimczak P, Schlaier J, Bogdahn U. TGF-β2 signaling in high-grade gliomas. Curr Pharm Biotech. 2011;12:2150-2157. [doi : 10.2174/138920111798808347](http://dx.doi.org/10.2174/138920111798808347)
55. Schaub NJ, Johnson CD, Cooper B, Gilbert RJ. Electrospun fibers for spinal cord injury research and regeneration, J Neurotrauma. 2016;33(15):1405-1415. doi: 1[0.1089/neu.2015.4165](https://doi.org/10.1089/neu.2015.4165)
56. Almeida SS, André F, Gonçalves GG, Completo, Marques PAAP. Stimulus responsive graphene scaffolds for tissue engineering. Carbon Nanostructure. 2016; 0(9783319456379): 219-256. doi: [10.1007/978-3-319-45639-3\_8](https://doi.org/10.1007/978-3-319-45639-3_8)
57. Alhodieb FS, Rahman MA, Barkat MA, Alanezi AA, Barkat HA, Hadi HA, et al. Nanomedicine-driven therapeutic interventions of autophagy and stem cells in the management of Alzheimer's disease. Nanomed. 2023; 18(2): 145-168. doi: 10.2217/nnm-2022-0108.
58. El-Husseiny HM, Mady EA, Doghish AS, Zewail MB, Abdelfatah AM, Noshy M. Smart/stimuli-responsive chitosan/gelatin and other polymeric macromolecules natural hydrogels vs. synthetic hydrogels systems for brain tissue engineering: A state-of-the-art review. Int J Biol Macromol. 2024;260(Pt 1):129323. doi: 10.1016/j.ijbiomac.2024.129323.
59. Li L, Guo Q, Liu Y, Lu M, Yang J, Ge Y, et al. Targeted combination therapy for glioblastoma by co-delivery of doxorubicin, YAP-siRNA and gold nanorods. J Material Sci Technol. 2021;63:81-90. [doi: 10.1016/j.jmst.2020.03.009](https://doi.org/10.1016/j.jmst.2020.03.009).
60. Alrushaid N, Khan FA, Al-Suhaimi EA, Elaissari A. Nanotechnology in cancer diagnosis and treatment. Pharmaceutics. 2023;15:1025. [doi: 10.3390/pharmaceutics15031025](https://doi.org/10.3390/pharmaceutics15031025)
61. Kaur K, Rai AK, Rustagi S. Recent advances in nanomaterial-based drug delivery systems. [Nano-Structures & Nano-Objects](https://www.sciencedirect.com/journal/nano-structures-and-nano-objects). 2024; 37:101103. [doi : 10.1016/j.nanoso.2024.101103](https://doi.org/10.1016/j.nanoso.2024.101103)
62. Salazar A, Pérez-de la Cruz V, Muñoz-Sandoval E, Chavarria V, Morales MG, Espinosa-Bonilla A, et al*.* Potential use of nitrogendoped carbon nanotube sponges as payload carriers against malignant glioma. Nanomaterials (Basel). 2021;11(5)*:*1244. doi: [10.3390/nano11051244](https://doi.org/10.3390/nano11051244)
63. Katti A, Diaz BJ, Caragine CM, Sanjana NE, Dow LE. CRISPR in cancer biology and therapy. Nature Rev Cancer*.* 2022;22:259–279. doi: 10.1038/s41568-022-00441-wet
64. Zhang P, Meng J, Li Y, Yang C, Hou Y, Tang W, et al. Nanotechnology-enhanced immunotherapy for metastatic cancer. The Innovation. 2021;2:100174. [doi: 10.1016/j.xinn.2021.10017](https://doi.org/10.1016/j.xinn.2021.10017)
65. [Shams](https://pubmed.ncbi.nlm.nih.gov/?term=Shams%20F%5BAuthor%5D) F, [Golchin](https://pubmed.ncbi.nlm.nih.gov/?term=Golchin%20A%5BAuthor%5D) A, [Azari](https://pubmed.ncbi.nlm.nih.gov/?term=Azari%20A%5BAuthor%5D) A, Mohammadi Amirabad L, Zarein F, Khosravi A, et al. Nanotechnology-based products for cancer immunotherapy. [Mol Biol Reports.](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8555726/)  2022; 49(2): 1389–1412. doi: [10.1007/s11033-021-06876-y](https://doi.org/10.1007/s11033-021-06876-y)
66. Zhu X, Li S. Nanomaterials in tumor immunotherapy: new strategies and challenges. Mol Cancer. 2023; 22:94. [doi: 10.1186/s12943-023-01797-9](https://doi.org/10.1186/s12943-023-01797-9).
67. Akabari A, Patel S, Vaghela N, Ramani V, Shah DP. Recent application of nanotechnology for cancer immunotherapy and its future prospects. [Int J Immunol Immunother](https://www.researchgate.net/journal/International-Journal-of-Immunology-and-Immunotherapy-2378-3672?_tp=eyJjb250ZXh0Ijp7ImZpcnN0UGFnZSI6InB1YmxpY2F0aW9uIiwicGFnZSI6InB1YmxpY2F0aW9uIiwicG9zaXRpb24iOiJwYWdlSGVhZGVyIn19). 2023; 10(1):1-17. doi: [10.23937/2378-3672/1410069](http://dx.doi.org/10.23937/2378-3672/1410069)
68. Yadav D, Puranik N, Meshram A, [Chavda](https://pubmed.ncbi.nlm.nih.gov/?term=Chavda+V&cauthor_id=36636642) V,  [Lee](https://pubmed.ncbi.nlm.nih.gov/?term=Lee+PC&cauthor_id=36636642) PC-W, [Jin](https://pubmed.ncbi.nlm.nih.gov/?term=Jin+JO&cauthor_id=36636642) J-O. How advanced are cancer immuno-nanotherapeutics? A comprehensive review of the literature. Int J Nanomed. 2023;18:35-48. [doi: 10.2147/IJN.S388349](https://doi.org/10.2147/IJN.S388349)
69. García-Domínguez DJ, López-Enríquez S,  Alba G, Garnacho C, Jiménez-Cortegana C, Flores-Campos R, et al*.* Cancer nano-immunotherapy: The novel and promising weapon to fight cancer. Int J Mol Sci. 2024;25(2):1195. [doi: 10.3390/ijms25021195](https://doi.org/10.3390/ijms25021195)
70. [Gharatape](https://pubs.rsc.org/en/results?searchtext=Author%3AAlireza%20Gharatape) A, [Sadeghi-Abandansari](https://pubs.rsc.org/en/results?searchtext=Author%3AHamid%20Sadeghi-Abandansari) H, [Seifalian](https://pubs.rsc.org/en/results?searchtext=Author%3AAlexander%20Seifalian) A, [Faridi-Majidi](https://pubs.rsc.org/en/results?searchtext=Author%3AReza%20Faridi-Majidi) R, [Basiri](https://pubs.rsc.org/en/results?searchtext=Author%3AMohsen%20Basiri) M. Nanocarrier-based gene delivery for immune cell engineering. **J Material Chem B. 2024; 12**:2917-2937. doi: [10.1039/d3tb02279j](https://doi.org/10.1039/d3tb02279j)
71. Chaturvedi VK, Singh A, Singh VK, Singh MP. [Cancer nanotechnology: A new revolution for cancer diagnosis and therapy.](https://pubmed.ncbi.nlm.nih.gov/30227814/) Curr Drug Metabol. 2019;20(6):416-429. [doi: 10.2174/1389200219666180918111528](https://doi.org/10.2174/1389200219666180918111528).
72. de Santana WMOS, Surur AK, Momesso VM, Lopes PM, Santilli CV, Fontana CR. [Nanocarriers for photodynamic-gene therapy.](https://pubmed.ncbi.nlm.nih.gov/37270046/)  Photodiagn Photodynam Ther. 2023;43: 103644. doi: 10.1016/j.pdpdt.2023.103644.
73. [Habeeb](https://pubs.rsc.org/en/results?searchtext=Author%3AMohammad%20Habeeb) M,  [Vengateswaran](https://pubs.rsc.org/en/results?searchtext=Author%3AHariharan%20Thirumalai%20Vengateswaran) HT,  [You](https://pubs.rsc.org/en/results?searchtext=Author%3AHuay%20Woon%20You) HW, [Saddhono](https://pubmed.ncbi.nlm.nih.gov/?term=Saddhono+K&cauthor_id=38288615) K, [Aher](https://pubmed.ncbi.nlm.nih.gov/?term=Aher+KB&cauthor_id=38288615) KB, Bhavar GB.  Nanomedicine facilitated cell signaling blockade: difficulties and strategies to overcome glioblastoma. J Mater Chem B. 2024;12:1677-1705. doi: [10.1039/d3tb02485g](https://doi.org/10.1039/d3tb02485g)
74. [Kang](https://pubmed.ncbi.nlm.nih.gov/?term=Kang+S&cauthor_id=32292496) S,   [Duan](https://pubmed.ncbi.nlm.nih.gov/?term=Duan+W&cauthor_id=32292496) W, [Zhang](https://pubmed.ncbi.nlm.nih.gov/?term=Zhang+S&cauthor_id=32292496) S,  [Chen](https://pubmed.ncbi.nlm.nih.gov/?term=Chen+D&cauthor_id=32292496) D,  [Feng](https://pubmed.ncbi.nlm.nih.gov/?term=Feng+J&cauthor_id=32292496) J,  [Qi](https://pubmed.ncbi.nlm.nih.gov/?term=Qi+N&cauthor_id=32292496) N. Muscone/RI7217 co-modified upward messenger DTX liposomes enhanced permeability of blood-brain barrier and targeting glioma. Theranostics. 2020;10(10):4308-4322. [doi: 10.7150/thno.41322](https://doi.org/10.7150/thno.41322)