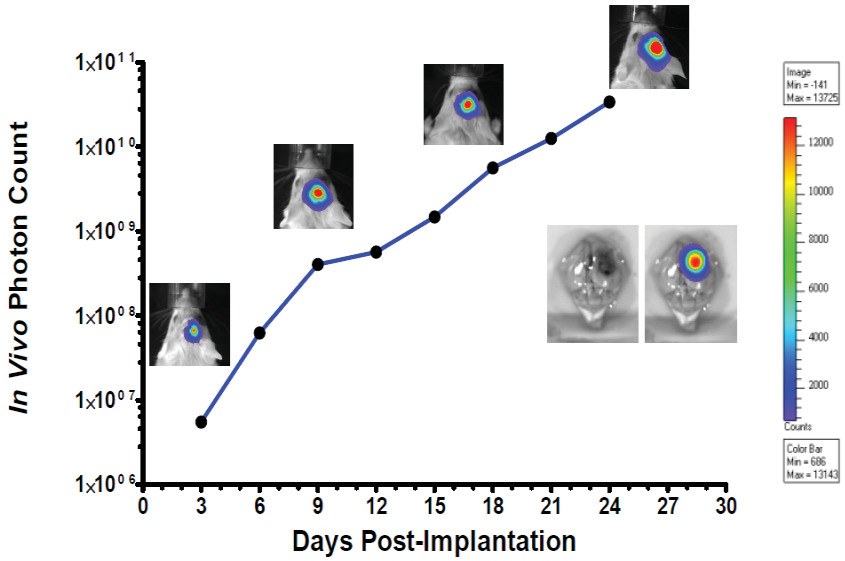
小动物活体光学成像技术在神经疾病研究中的应用

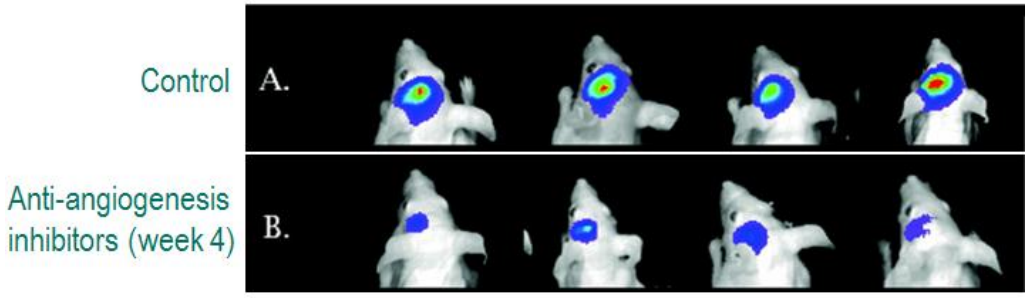
Revvity小动物活体光学成像技术已在生命科学基础研究、临床前医学研究及药物研发等领域得到广泛应用。在众多应用领域中，神经疾病研究是活体光学成像技术的应用热点之一。在应用活体光学成像技术进行神经相关疾病研究中，常用的标记方法及应用领域包括：1、利用萤火虫荧光素酶（Firefly Luciferase）或荧光蛋白作为报告基因，通过转基因技术体外转染神经肿瘤细胞、神经干细胞等细胞，进行神经肿瘤、神经发育及细胞治疗的相关研究；2、利用荧光素酶作为报告基因标记神经疾病相关基因构建转基因动物，进行神经疾病机理研究；3、利用功能性荧光探针监测神经疾病的发生发展。下面结合一些具体实例进行阐述：

一.神经肿瘤研究

与其它类型肿瘤研究类似，利用小动物活体光学成像技术可以长期监测神经肿瘤的发生发展及治疗效果。例如，利用荧光素酶基因标记肿瘤细胞，通过肿瘤发光情况的变化，观测肿瘤的生长及药物对于肿瘤的治疗效果，如下：

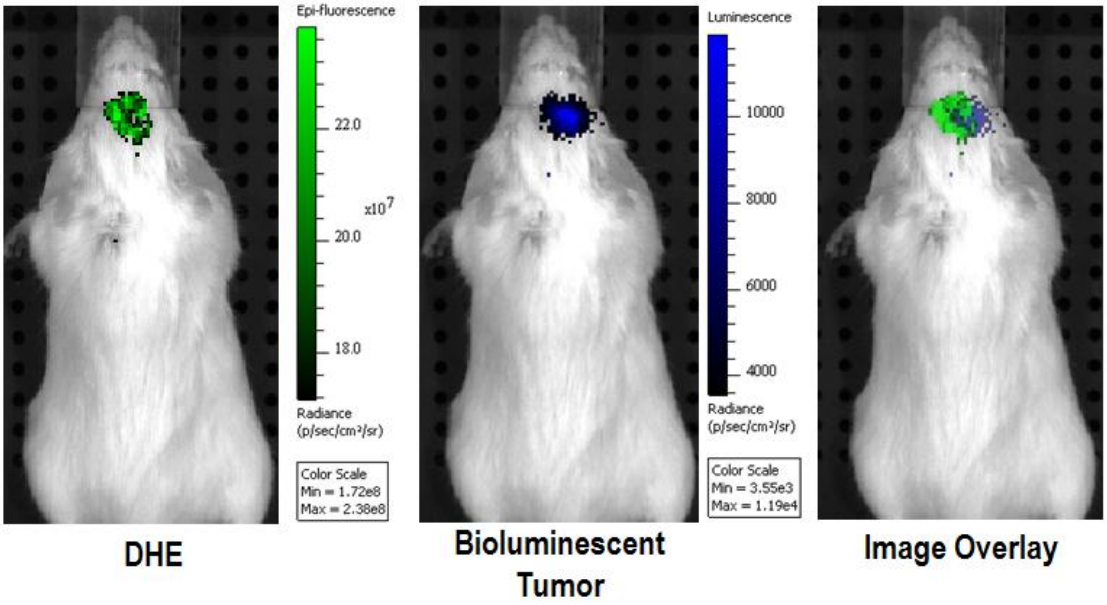


上图：应用 IVIS 系统长期观测原位接种的经生物发光标记的 U87-MG-luc2 神经胶质瘤的生长。



上图：应用 IVIS 系统观测血管生成抑制剂对 U87-MG-luc2 生长的移植。A.对照组；B.给药组

除了利用生物发光成像技术进行神经肿瘤研究，还可应用功能性荧光探针监测肿瘤，例如，通过应用荧光染料标记的 DHE 探测神经胶质瘤中的活性氧自由基，从而监测肿瘤的发展情况。基于 IVIS 系统的多模式成像功能，可以同时应用生物发光及荧光成像功能共同监测肿瘤，如下：



上图：左.应用荧光成像技术观测尾静脉注射 DHE 后观测 DHE 对肿瘤的靶向；中.应用生物发光成像技术观测经荧光素酶基因标记的肿瘤；右.荧光与生物发光成像结果融合。

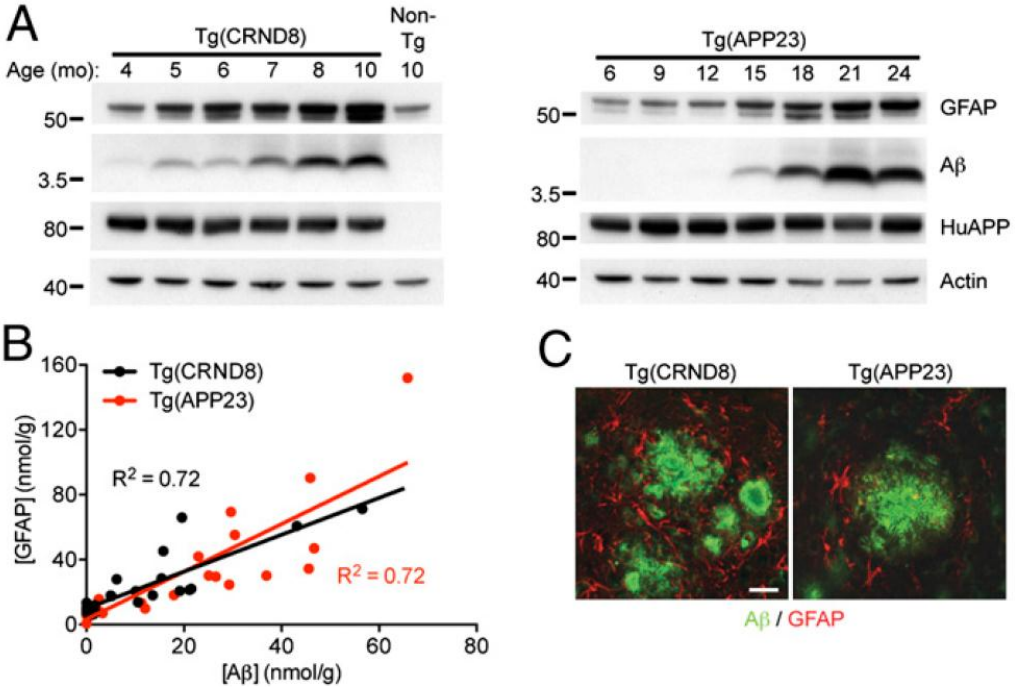
二.神经退行性疾病的研究

神经退行性疾病是由神经元或其髓鞘的丧失所致，随着时间的推移而恶化，以导致功能障碍。常见的神经退行性疾病包括阿兹海默症、帕金森氏病、多发性硬化症、脊髓性肌萎缩症等。应用小动物活体成像技术进行上述疾病相关研究的主要方式为：1、通过构建生物发光标记的疾病动物模型，观测疾病特异性基因的表达，进而反映疾病的发生发展；2、应用功能性荧光探针观测疾病特异性标识物，进而反映疾病的发生发展。下面以阿兹海默症的研究为例进行阐述：

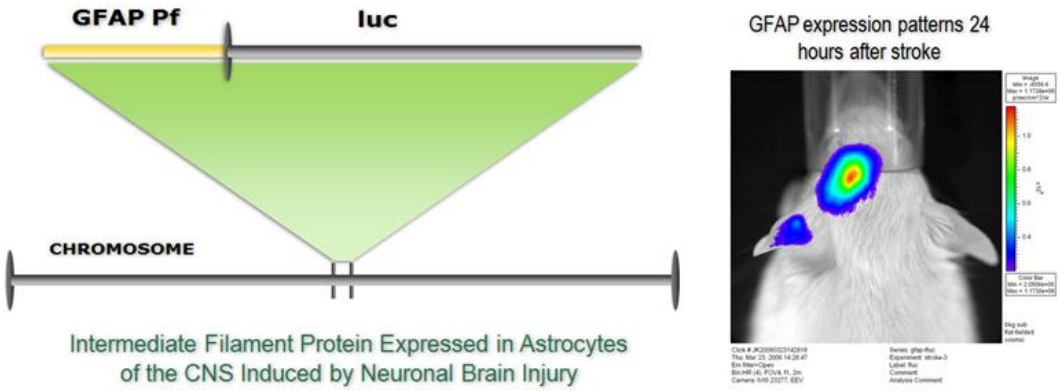
阿兹海默症（Alzheimer disease，AD），是一种中枢神经系统变性病。AD 的病因及发病机制尚未阐明，特征性病理改变为 β 淀粉样蛋白沉积形成的细胞外老年斑和 tau 蛋白过度磷酸化形成的神经细胞内神经原纤维缠结，以及神经元丢失伴随胶质细胞增生等。基于特殊的病理特征，研究者可以通过不同思路应用活体光学成像技术，对阿兹海默症进行观测。

如 Wattnoek 等人基于阿兹海默症的发生伴随胶质细胞增生的病理特征推测，伴随阿兹海默症的发生发展，胶质细胞中胶质纤维酸性蛋白（glial fibrillary acidic protein, GFAP）的表达量也会增多。利用 Western Blot 及免疫组化等技术手段进行体外实验显示，随着 β 淀粉样蛋白表达的增多，GFAP 的表达量也同时增多，两者在疾病发展过程中成

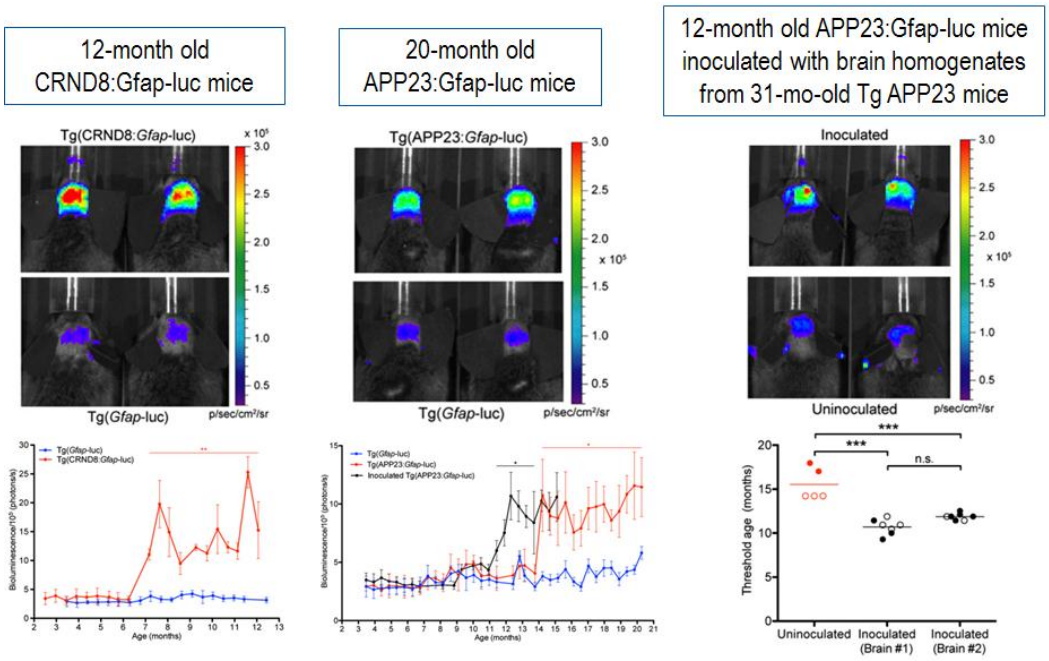
正相关，说明 GFAP 可以作为阿兹海默症的特征性蛋白而反映阿兹海默症的发生发展。接着，研究者将 Tg(GFAP-luc)生物发光转基因小鼠与阿兹海默疾病模型小鼠 Tg(APP23)及 Tg(CRND8)进行杂交，构建出 Tg(APP23:Gfap-luc) 和 Tg(CRND8:Gfap-luc)双转基因生物发光-阿兹海默疾病模型小鼠，并应用 IVIS 系统在活体水平观测阿兹海默症的发生发展。结果显示，在两种双转基因疾病模型小鼠中，GFAP 的表达量均随阿兹海默症病情的恶化而升高，说明 GFAP 可以表征阿兹海默症的发生发展；另外，将病情严重的老年疾病小鼠脑匀浆注射入年轻疾病小鼠脑内，会使年轻疾病小鼠中 GFAP 表达量的增多明显提前，说明老年疾病小鼠脑匀浆物质能够加速年轻疾病小鼠阿兹海默症的发生。综上所述，通过利用荧光素酶标记疾病相关基因而构建的转基因小鼠，并结合活体光学成像技术，可以在活体水平观测神经退行性疾病的发生发展，并开展相关治疗的研究。



上图：体外分析 GFAP 的表达与阿兹海默症的关系。A.应用 Western blot 技术分析 GFAP 及 Aβ 在不同年龄的两种阿兹海默疾病模型小鼠中的表达情况；B.定量分析显示 GFAP 与 Aβ 的表达成正相关；C.应用免疫组化技术分析 GFAP 与 Aβ 在阿兹海默疾病模型小鼠中的表达情况。

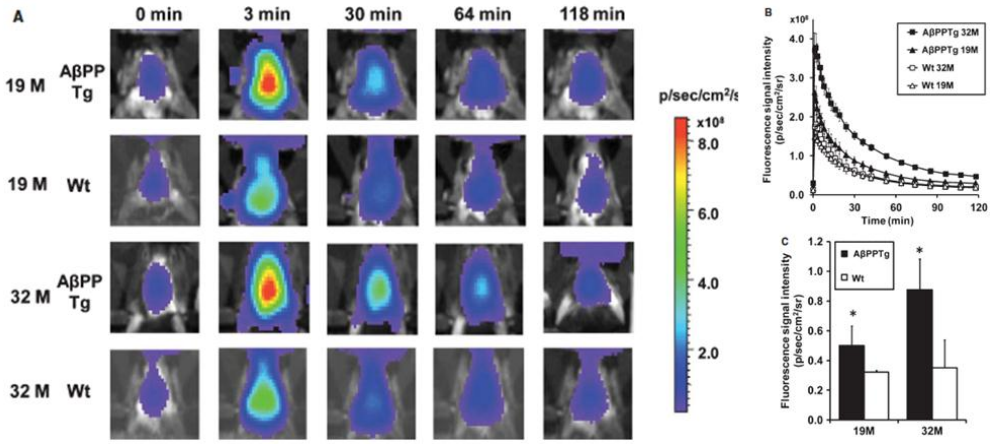


上图：Tg(GFAP-luc)生物发光转基因小鼠构建示意图及活体成像结果。



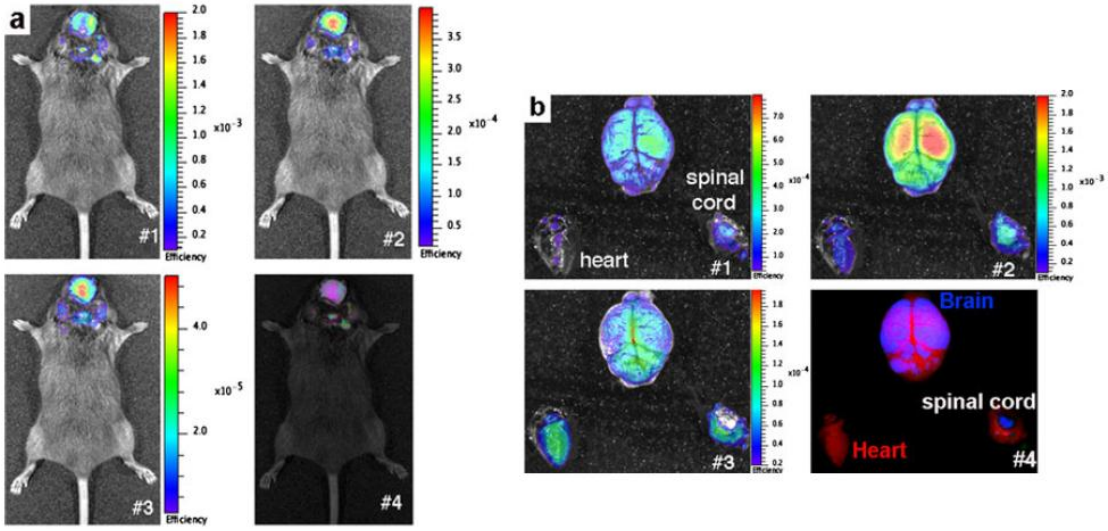
上图：应用 GFAPTg(APP23:Gfap-luc) 和 Tg(CRND8:Gfap-luc)双转基因生物发光-阿兹海默疾病模型小鼠，结合生物发光活体成像技术，观测阿兹海默症的发生发展。

随着荧光功能性探针的发展，研究者除了可以应用生物发光活体成像技术研究神经退行性疾病，还可应用活体荧光成像技术开展该方面研究。目前科研人员已开发出一些有效的荧光功能性探针，它们通过尾静脉注射后能够顺利通过血脑屏障，并特异性靶向结合 β 淀粉样蛋白，通过荧光信号监测脑中 β 淀粉样蛋白的含量，进而反映阿兹海默症的发生发展。Okamura 等人报道，他们利用自己研发的荧光探针 THK-265，在活体水平成功观测到阿兹海默疾病模型小鼠脑部 β 淀粉样蛋白的沉积。如下图所示，将 THK-265 尾静脉注射入 19 个月及 32 个月的阿兹海默疾病模型小鼠 Tg(APP23)体内，利用 IVIS 系统观测不同时间点 THK-265 在脑部的信号，结果显示，与未发生阿兹海默症的正常小鼠相比，疾病模型小鼠脑部的荧光信号均较高，表明 THK-265 能够有效探测疾病模型小鼠脑部更多的 β 淀粉样蛋白沉积；而与 19 个月的疾病小鼠相比，32 个月的疾病小鼠脑部的荧光信号更高，表明 32 个月的疾病小鼠患病程度更严重。



上图：A.利用 IVIS 系统观测不同时间点 THK-265 在脑部的荧光信号；B/C.定量分析结果。

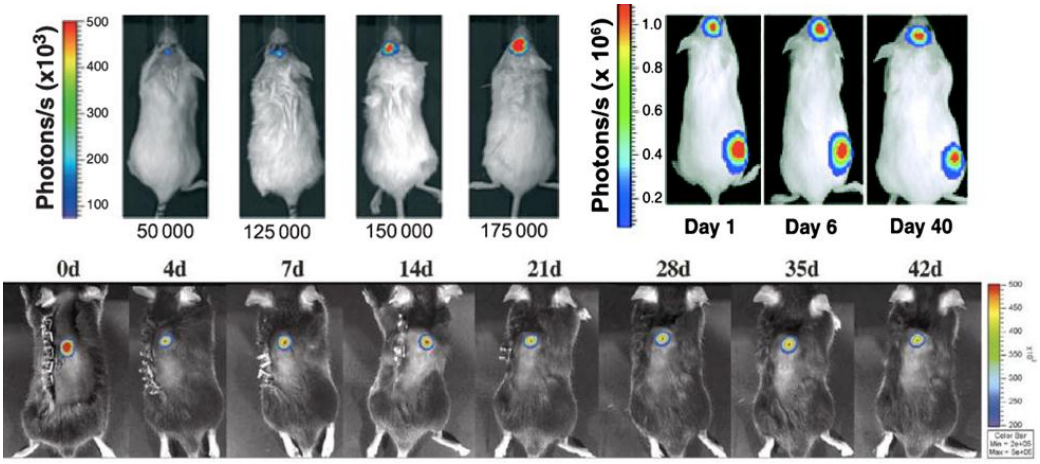
Ran 等报道了利用他们自行研发的基于姜黄素的荧光探针 CRANAD-3，进行 β 淀粉样蛋白的活体观测。CRANAD-3 探针本身具有荧光性，有趣的是，当探针未与 Aβ 结合时，其最大吸收峰为 700nm，而一旦与 Aβ 结合，其最大吸收峰将会蓝移至 640nm。利用探针的这一特性，研究者不但可以观测到患有阿兹海默症的小鼠脑中更多的 Aβ 沉积，而且可以利用 IVIS 系统的光谱分离技术，区分与 Aβ 特异性结合的探针及未与 Aβ 结合的游离探针，进而获得更准确的成像及定量分析结果。



上图：利用 IVIS 系统的光谱分离技术观测 CRANAD-3 探针在阿兹海默疾病模型小鼠 Tg(APP23)脑中的荧光信号。a.活体成像光谱分离结果；b.将整个脑部取出后的，体外脑部成像光谱分离结果。(#1)自发荧光信号，(#2)与 Aβ 特异性结合的探针信号，(#3)游离的非特异性探针信号，(#4)上述三种信号的融合影像。

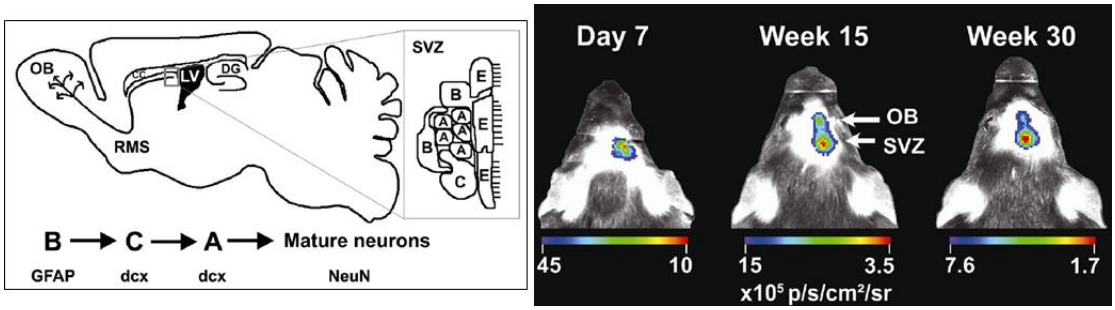
三.神经干细胞研究

与其它类型干细胞研究类似，应用小动物活体光学成像技术，可以在活体水平监测神经干细胞的移植、存活和增殖，以及示踪干细胞在体内的分布和迁移。由于神经疾病发生的部位主要集中于颅内及脊髓等相对较深的区域，而生物发光成像技术的极高灵敏度使得神经干细胞在上述区域的观测成为可能。下图所示为利用生物发光成像技术，对神经干细胞在颅内或脊髓移植后的存活及增殖进行长期观测。



上图：利用 IVIS 系统长期观测神经干细胞体内移植后的存活及增殖。A.颅内移植；B.脊髓移植。

干细胞移植后，活体示踪干细胞的分布和迁徙具有重要意义。通过示踪，不仅可以直观地了解其在体内的分布，而且可以追踪到其体内的分化转归及调控机制。神经干细胞增殖及迁移的缺陷是造成帕金森氏病等神经退行性疾病的主要原因。神经干细胞起源于侧脑室外侧壁的室管膜下层区域（subventricular zone，SVZ）与海马齿状回（dentate gyrus，DG），之后通过嘴侧迁移流（rostral migratory stream，RMS）到达嗅球（olfactory bulb，OB），进一步分化为中枢神经细胞并融入现有的神经通路。2008 年发表于 Stem Cell 上的一篇文献报道了利用生物发光成像技术观测神经干细胞的上述迁移情况。如下图所示：

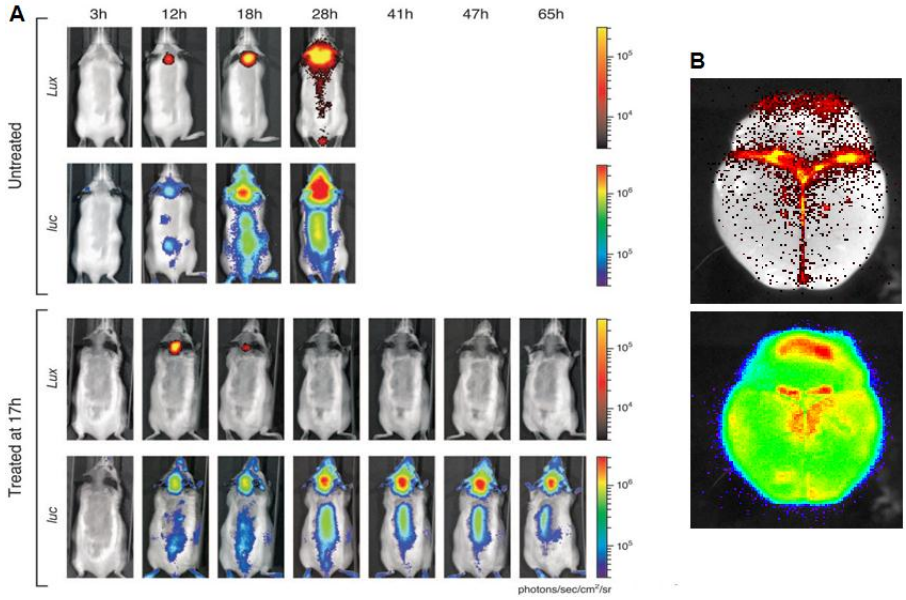


上图左：神经干细胞迁移示意图；上图右：将经生物发光标记的神经干细胞直接注入小鼠颅内 SVZ 区域，利用 IVIS 系统观测神经干细胞在颅内的迁移。

四.研究神经疾病中相关基因的表达

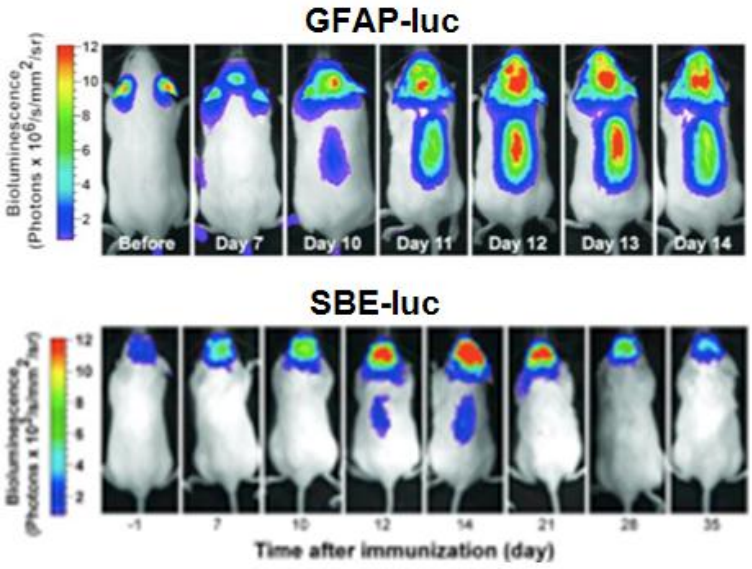
对于神经疾病中相关特异性基因的研究，可以揭示神经疾病的分子机理，更好的了解神经疾病的发生发展及相关治疗。小动物活体光学成像技术已越来越多的应用于此类研究。研究者通过构建各种生物发光转基因动物，结合活体光学成像技术，在活体动物水平观测神经疾病发展过程中相关基因的表达。

Cordeau 等利用 Tg(GFAP-luc)转基因小鼠，监测 GFAP 在肺炎链球菌感染而引发的脑膜炎中的表达。研究者用细菌荧光素酶（bacterial luciferase）基因标记肺炎链球菌，以监测细菌在活体动物体内的感染情况，同时以萤火虫荧光素酶基因标记的 Tg(GFAP-luc)转基因小鼠为实验动物，观测 GFAP 在肺炎链球菌感染而引发的脑膜炎中的表达，以及经抗生素治疗后细菌的感染情况和 GFAP 的表达情况。结果显示，随着细菌感染程度及范围的升高和扩大，GFAP 的表达量也相应升高；而经抗生素治疗后，细菌的感染情况明显被抑制，GFAP 的表达量也随之降低。对小鼠感染脑部的体外成像结果显示，细菌对于脑部局部区域的感染，能引发整个脑部 GFAP 的大量表达。



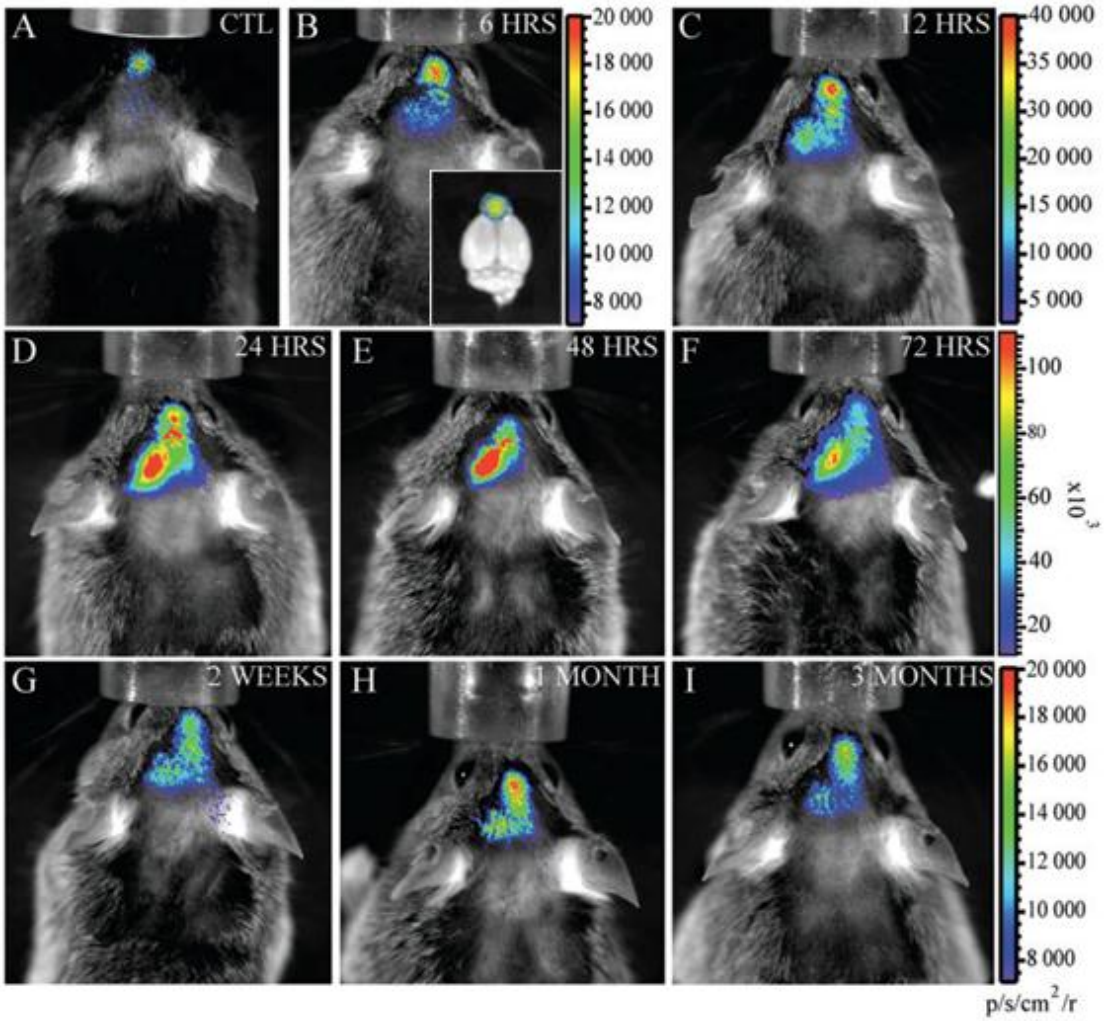
上图：应用 IVIS 系统观测肺炎链球菌在 Tg(GFAP-luc)转基因小鼠中的感染情况及 GFAP 的表达情况。A. 活体成像结果，untreated：未经抗生素治疗，treated：经抗生素治疗；B.脑部体外成像结果。

Luo 等利用 Tg(GFAP-luc)及 Tg(SBE-luc) 转基因小鼠，结合活体光学成像技术，观测了在自身免疫性脑脊髓炎（EAE）中与 GFAP 表达相关的星形胶质细胞的聚集及与 TGF-β 信号通路相关的炎症的发生。研究者用髓磷脂少突细胞糖蛋白（MOG）免疫小鼠，引发实验性自身免疫性脑脊髓炎，随后，利用 IVIS 系统观测患病 Tg(GFAP-luc)及 Tg(SBE-luc)转基因小鼠中 GFAP 及 TGF-β 的表达情况。结果显示，小鼠免疫后的第 7 天，即可观测到 GFAP 及 TGF-β 表达量显著升高，说明在脑脊髓炎的发病初期，即伴随有星形胶质细胞的聚集以及炎症的发生。值得注意的是，脑脊髓炎的明显临床症状出现于免疫后 11 天，因此，与观察临床症状而诊断疾病发生的方法相比，通过应用活体光学成像技术观测疾病相关基因的表达，能够更早的观测到疾病的发生。



上图：应用 IVIS 系统观测自身免疫性脑脊髓炎小鼠中 GFAP 及 TGF-β 的表达情况。（上）应用 Tg(GFAP-luc)转基因小鼠观测 GFAP 的表达；（下）应用 Tg(SBE-luc)转基因小鼠观测 TGF-β 的表达。

Lalancette-Herbert 等利用 Tg(TLR2-luc) 转基因小鼠，结合活体光学成像技术，观测了小胶质细胞中 Toll-like receptor 2 (TLR2)在大脑中动脉闭塞（MCAO）导致的脑缺血损伤模型中的表达情况，发现脑缺血损伤会激活小胶质细胞，引起 TLR2 的长期大量表达（可持续数月），并且 TLR2 的表达不仅存在于脑部发生缺血损伤的区域，而且存在于嗅球中，说明嗅球中的小胶质细胞在神经性炎症中起重要调节作用。



上图：应用 Tg(TLR2-luc) 转基因小鼠结合 IVIS 系统，观测 TLR2 在脑缺血损伤模型中的长期表达。

IVIS APPLICATIONS IN NEUROSCIENCE RESEARCH

1. Ahmed N, Ratnayake M, Savoldo B, Perlaky L, Dotti G, Wels WS, Bhattacharjee MB, Gilbertson RJ, Shine HD, Weiss HL, Rooney CM, Heslop HE, Gottschalk S. Regression of experimental medulloblastoma following transfer of HER2-specific T cells. *Cancer research.* Jun 15 2007;67(12):5957-5964.

2. Ahmed N, Salsman VS, Kew Y, Shaffer D, Powell S, Zhang YJ, Grossman RG, Heslop HE, Gottschalk S. HER2-specific T cells target primary glioblastoma stem cells and induce regression of autologous experimental tumors. *Clin Cancer Res.* Jan 15 2010;16(2):474-485.

3. Akens MK, Yee AJ, Wilson BC, Burch S, Johnson CL, Lilge L, Bisland SK. Photodynamic therapy of vertebral metastases: evaluating tumor-to-neural tissue uptake of BPD-MA and ALA-PpIX in a murine model of metastatic human breast carcinoma. *Photochemistry and photobiology.* Sep-Oct 2007;83(5):1034-1039.

4. Alizadeh D, Zhang L, Brown CE, Farrukh O, Jensen MC, Badie B. Induction of anti-glioma natural killer cell response following multiple low-dose intracerebral CpG therapy. *Clin Cancer Res.* Jul 1 2010;16(13):3399-3408.

5. Amante FH, Stanley AC, Randall LM, Zhou Y, Haque A, McSweeney K, Waters AP, Janse CJ, Good MF, Hill GR, Engwerda CR. A role for natural regulatory T cells in the pathogenesis of experimental cerebral malaria. *The American journal of pathology.* Aug 2007;171(2):548-559.

6. Aravalli RN, Hu S, Lokensgard JR. Inhibition of toll-like receptor signaling in primary murine microglia. *J Neuroimmune Pharmacol.* Mar 2008;3(1):5-11.

7. Aravalli RN, Hu S, Woods JP, Lokensgard JR. Histoplasma capsulatum yeast phase-specific protein Yps3p induces Toll-like receptor 2 signaling. *Journal of neuroinflammation.* 2008;5:30.

8. Baia GS, Dinca EB, Ozawa T, Kimura ET, McDermott MW, James CD, Vandenberg SR, Lal A. An Orthotopic Skull Base Model of Malignant Meningioma. *Brain Pathol.* Dec 17 2007.

9. Becher OJ, Hambardzumyan D, Fomchenko EI, Momota H, Mainwaring L, Bleau AM, Katz AM, Edgar M, Kenney AM, Cordon-Cardo C, Blasberg RG, Holland EC. Gli activity correlates with tumor grade in platelet-derived growth factor-induced gliomas. *Cancer research.* Apr 1 2008;68(7):2241-2249.

10. Benaron DA, Contag PR, Contag CH. Imaging brain structure and function, infection and gene expression in the body using light. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences.* June 1997;352(1354):755-761.

11. Bertino P, Piccardi F, Porta C, Favoni R, Cilli M, Mutti L, Gaudino G.

Imatinib mesylate enhances therapeutic effects of gemcitabine in human malignant mesothelioma xenografts. *Clin Cancer Res.* Jan 15 2008;14(2):541-548.

12. Black KL, Yin D, Ong JM, Hu J, Konda BM, Wang X, Ko MK, Bayan JA, Sacapano MR, Espinoza A, Irvin DK, Shu Y. PDE5 inhibitors enhance tumor permeability and efficacy of chemotherapy in a rat brain tumor model. *Brain research.* Sep 16 2008;1230:290-302.

13. Bos PD, Zhang XH, Nadal C, Shu W, Gomis RR, Nguyen DX, Minn AJ, van de Vijver MJ, Gerald WL, Foekens JA, Massague J. Genes that mediate breast cancer metastasis to the brain. *Nature.* Jun 18 2009;459(7249):1005-1009.

14. Bradbury MS, Tomishima M, Panagiotakos G, Chan BK, Zanzonico P, Vider J, Ponomarev V, Studer L, Tabar V. Optical bioluminescence imaging of human ES cell progeny in the rodent CNS. *J Neurochem.* Jun 7 2007.

15. Bryant MJ, Chuah TL, Luff J, Lavin MF, Walker DG. A novel rat model for glioblastoma multiforme using a bioluminescent F98 cell line. *J Clin Neurosci.* May 2008;15(5):545-551.

16. Burgos JS, Rosol M, Moats RA, Khankaldyyan V, Kohn DB, Nelson MD, Jr., Laug WE. Time course of bioluminescent signal in orthotopic and heterotopic brain tumors in nude mice. *Biotechniques.* June 2003;34(6):1184-1188.

17. Calabrese C, Poppleton H, Kocak M, Hogg TL, Fuller C, Hamner B, Oh EY, Gaber MW, Finklestein D, Allen M, Frank A, Bayazitov IT, Zakharenko SS, Gajjar A, Davidoff A, Gilbertson RJ. A perivascular niche for brain tumor stem cells. *Cancer Cell.* Jan 2007;11(1):69-82.

18. Chaudhari AJ, Darvas F, Bading JR, Moats RA, Conti PS, Smith DJ, Cherry SR, Leahy RM. Hyperspectral and multispectral bioluminescence optical tomography for small animal imaging. *Phys Med Biol.* Dec 7 2005;50(23):5421-5441.

19. Chen X, Conti PS, Moats RA. In vivo near-infrared fluorescence imaging of integrin alphavbeta3 in brain tumor xenografts. *Cancer research.* November 2004;64(21):8009-8014.

20. Cheng Z, Wu Y, Xiong Z, Gambhir SS, Chen X. Near-infrared fluorescent RGD peptides for optical imaging of integrin alphavbeta3 expression in living mice. *Bioconjug Chem.* Nov-Dec 2005;16(6):1433-1441.

21. Cook SH, Griffin DE. Luciferase imaging of a neurotropic viral infection in intact animals. *Journal of virology.* May 2003;77(9):5333-5338.

22. Cordeau P, Jr., Lalancette-Hebert M, Weng YC, Kriz J. Live imaging of neuroinflammation reveals sex and estrogen effects on astrocyte response to ischemic injury. *Stroke; a journal of cerebral circulation.* Mar 2008;39(3):935-942.

23. Couillard-Despres S, Finkl R, Winner B, Ploetz S, Wiedermann D,

Aigner R, Bogdahn U, Winkler J, Hoehn M, Aigner L. In vivo optical imaging of neurogenesis: watching new neurons in the intact brain. *Mol Imaging.* Jan-Feb 2008;7(1):28-34.

24. Daadi MM, Davis AS, Arac A, Li Z, Maag AL, Bhatnagar R, Jiang K, Sun G, Wu JC, Steinberg GK. Human neural stem cell grafts modify microglial response and enhance axonal sprouting in neonatal hypoxic-ischemic brain injury. *Stroke; a journal of cerebral circulation.* Mar 2010;41(3):516-523.

25. Daneshvar H, Nelms J, Muhammad O, Jackson H, Tkach J, Davros W, Peterson T, Vogelbaum MA, Bruchez MP, Toms SA. Imaging characteristics of zinc sulfide shell, cadmium telluride core quantum dots. *Nanomedicine (London, England).* Feb 2008;3(1):21-29.

26. Dellacasa-Lindberg I, Hitziger N, Barragan A. Localized recrudescence of Toxoplasma infections in the central nervous system of immunocompromised mice assessed by in vivo bioluminescence imaging. *Microbes Infect.* Sep 2007;9(11):1291-1298.

27. Deroose CM, Reumers V, Gijsbers R, Bormans G, Debyser Z, Mortelmans L, Baekelandt V. Noninvasive Monitoring of Long-Term Lentiviral Vector-Mediated Gene Expression in Rodent Brain with Bioluminescence Imaging. *Molecular Therapy.* 2006;In Press, Corrected Proof.

28. Dickson PV, Hamner JB, Burger RA, Garcia E, Ouma AA, Kim SU, Ng CY, Gray JT, Aboody KS, Danks MK, Davidoff AM. Intravascular administration of tumor tropic neural progenitor cells permits targeted delivery of interferon-beta and restricts tumor growth in a murine model of disseminated neuroblastoma. *Journal of pediatric surgery.* Jan 2007;42(1):48-53.

29. Dickson PV, Hamner JB, Cauthen LA, Ng CY, McCarville MB, Davidoff AM. Efficacy of zoledronate against neuroblastoma. *Surgery.* Aug 2006;140(2):227-235.

30. Dinca EB, Lu KV, Sarkaria JN, Pieper RO, Prados MD, Haas-Kogan DA, Vandenberg SR, Berger MS, James CD. p53 Small-molecule inhibitor enhances temozolomide cytotoxic activity against intracranial glioblastoma xenografts. *Cancer research.* Dec 15 2008;68(24):10034-10039.

31. Dohlen G, Carlsen H, Blomhoff R, Thaulow E, Saugstad OD. Reoxygenation of Hypoxic Mice with 100% Oxygen Induces Brain Nuclear Factor-kappa B. *Pediatr Res.* November 1, 2005 2005;58(5):941-945.

32. Dohlen G, Odland HH, Carlsen H, Blomhoff R, Thaulow E, Saugstad OD. Antioxidant activity in the newborn brain: a luciferase mouse model. *Neonatology.* 2008;93(2):125-131.

33. Doubrovin M, Serganova I, Mayer-Kuckuk P, Ponomarev V, Blasberg RG. Multimodality in vivo molecular-genetic imaging. *Bioconjugate*

Chemistry. Nov-December 2004;15(6):1376-1388.

34. Douma S, Van Laar T, Zevenhoven J, Meuwissen R, Van Garderen E, Peeper DS. Suppression of anoikis and induction of metastasis by the neurotrophic receptor TrkB. *Nature.* August 2004;430(7003):1034-1039.

35. Dugger KJ, Zinn KR, Weaver C, Bullard DC, Barnum SR. Effector and suppressor roles for LFA-1 during the development of experimental autoimmune encephalomyelitis. *Journal of neuroimmunology.* Jan 3 2009;206(1-2):22-27.

36. Echchannaoui H, Frei K, Schnell C, Leib SL, Zimmerli W, Landmann R. Toll-like receptor 2-deficient mice are highly susceptible to Streptococcus pneumoniae meningitis because of reduced bacterial clearing and enhanced inflammation. *Journal of Infectious Disease.* September 2002;186(6):798-806.

37. Ezhilarasan R, Jadhav U, Mohanam I, Rao JS, Gujrati M, Mohanam S. The hemopexin domain of MMP-9 inhibits angiogenesis and retards the growth of intracranial glioblastoma xenograft in nude mice. *International journal of cancer.* Jan 15 2009;124(2):306-315.

38. Fujita M, Lee BS, Khazenzon NM, Penichet ML, Wawrowsky KA, Patil R, Ding H, Holler E, Black KL, Ljubimova JY. Brain tumor tandem targeting using a combination of monoclonal antibodies attached to biopoly(beta-L-malic acid). *J Control Release.* Oct 8 2007;122(3):356-363.

39. Garzia L, Andolfo I, Cusanelli E, Marino N, Petrosino G, De Martino D, Esposito V, Galeone A, Navas L, Esposito S, Gargiulo S, Fattet S, Donofrio V, Cinalli G, Brunetti A, Vecchio LD, Northcott PA, Delattre O, Taylor MD, Iolascon A, Zollo M. MicroRNA-199b-5p impairs cancer stem cells through negative regulation of HES1 in medulloblastoma. *PLoS ONE.* 2009;4(3):e4998.

40. Gerdoni E, Gallo B, Casazza S, Musio S, Bonanni I, Pedemonte E, Mantegazza R, Frassoni F, Mancardi G, Pedotti R, Uccelli A. Mesenchymal stem cells effectively modulate pathogenic immune response in experimental autoimmune encephalomyelitis. *Annals of neurology.* Mar 2007;61(3):219-227.

41. Ghods AJ, Irvin D, Liu G, Yuan X, Abdulkadir IR, Tunici P, Konda B, Wachsmann-Hogiu S, Black KL, Yu JS. Spheres isolated from 9L gliosarcoma rat cell line possess chemoresistant and aggressive cancer stem-like cells. *Stem cells (Dayton, Ohio).* Jul 2007;25(7):1645-1653.

42. Goldhoff P, Warrington NM, Limbrick DD, Jr., Hope A, Woerner BM, Jackson E, Perry A, Piwnica-Worms D, Rubin JB. Targeted inhibition of cyclic AMP phosphodiesterase-4 promotes brain tumor regression. *Clin Cancer Res.* Dec 1 2008;14(23):7717-7725.

43. Gondi CS, Veeravalli KK, Gorantla B, Dinh DH, Fassett D, Klopfenstein JD, Gujrati M, Rao JS. Human umbilical cord blood stem cells show

PDGF-D-dependent glioma cell tropism in vitro and in vivo. *Neuro-oncology.* May 2010;12(5):453-465.

44. Greene IP, Lee EY, Prow N, Ngwang B, Griffin DE. Protection from fatal viral encephalomyelitis: AMPA receptor antagonists have a direct effect on the inflammatory response to infection. *Proceedings of the National Academy of Sciences of the United States of America.* Mar 4 2008;105(9):3575-3580.

45. Hamner JB, Dickson PV, Sims TL, Zhou J, Spence Y, Ng CY, Davidoff AM. Bortezomib inhibits angiogenesis and reduces tumor burden in a murine model of neuroblastoma. *Surgery.* Aug 2007;142(2):185-191.

46. Hashizume R, Gupta N, Berger MS, Banerjee A, Prados MD, Ayers-Ringler J, James CD, VandenBerg SR. Morphologic and molecular characterization of ATRT xenografts adapted for orthotopic therapeutic testing. *Neuro-oncology.* Apr 2010;12(4):366-376.

47. Hashizume R, Ozawa T, Dinca EB, Banerjee A, Prados MD, James CD, Gupta N. A human brainstem glioma xenograft model enabled for bioluminescence imaging. *Journal of neuro-oncology.* Jul 8 2009.

48. Hata N, Shinojima N, Gumin J, Yong R, Marini F, Andreeff M, Lang FF. Platelet-derived growth factor BB mediates the tropism of human mesenchymal stem cells for malignant gliomas. *Neurosurgery.* Jan 2010;66(1):144-156; discussion 156-147.

49. Hatton BA, Villavicencio EH, Tsuchiya KD, Pritchard JI, Ditzler S, Pullar B, Hansen S, Knoblaugh SE, Lee D, Eberhart CG, Hallahan AR, Olson JM. The Smo/Smo model: hedgehog-induced medulloblastoma with 90% incidence and leptomeningeal spread. *Cancer research.* Mar 15 2008;68(6):1768-1776.

50. Hauck ES, Zou S, Scarfo K, Nantz MH, Hecker JG. Whole animal in vivo imaging after transient, nonviral gene delivery to the rat central nervous system. *Mol Ther.* Nov 2008;16(11):1857-1864.

51. Heikkila JE, Vaha-Koskela MJ, Ruotsalainen JJ, Martikainen MW, Stanford MM, McCart JA, Bell JC, Hinkkanen AE. Intravenously administered alphavirus vector VA7 eradicates orthotopic human glioma xenografts in nude mice. *PLoS ONE.* 2010;5(1):e8603.

52. Ho G, Kumar S, Zhang C, Kng YL, Zhuo L. Molecular imaging reveals a correlation between 2'-CH3-MPTP-induced neonatal neurotoxicity and dopaminergic neurodegeneration in adult transgenic mice. *Int J Dev Neurosci.* Nov 2008;26(7):673-681.

53. Ho G, Zhang C, Zhuo L. Non-invasive fluorescent imaging of gliosis in transgenic mice for profiling developmental neurotoxicity. *Toxicology and applied pharmacology.* May 15 2007;221(1):76-85.

54. Hoehn M, Himmelreich U, Kruttwig K, Wiedermann D. Molecular and cellular MR imaging: potentials and challenges for neurological applications. *J Magn Reson Imaging.* May 2008;27(5):941-954.

55. Hsu AR, Hou L, A V, Greve J, V H, V T, X C. In Vivo Near-Infrared

Fluorescence Imaging of Integrin alpha V beta 3 in an Orthotopic Glioblastoma Model. *Molecular Imaging and BIology.* 2006.

56. Hsu AR, Cai W, Veeravagu A, Mohamedali KA, Chen K, Kim S, Vogel H, Hou LC, Tse V, Rosenblum MG, Chen X. Multimodality molecular imaging of glioblastoma growth inhibition with vasculature-targeting fusion toxin VEGF121/rGel. *J Nucl Med.* Mar 2007;48(3):445-454.

57. Hu J, Ljubimova JY, Inoue S, Konda B, Patil R, Ding H, Espinoza A, Wawrowsky KA, Patil C, Ljubimov AV, Black KL. Phosphodiesterase type 5 inhibitors increase Herceptin transport and treatment efficacy in mouse metastatic brain tumor models. *PLoS ONE.* 2010;5(4):e10108.

58. Hutter E, Boridy S, Labrecque S, Lalancette-Hebert M, Kriz J, Winnik FM, Maysinger D. Microglial response to gold nanoparticles. *ACS nano.* May 25 2010;4(5):2595-2606.

59. Huysentruyt LC, Mukherjee P, Banerjee D, Shelton LM, Seyfried TN. Metastatic cancer cells with macrophage properties: evidence from a new murine tumor model. *International journal of cancer.* Jul 1 2008;123(1):73-84.

60. Hwang DW, Jang SJ, Kim YH, Kim HJ, Shim IK, Jeong JM, Chung JK, Lee MC, Lee SJ, Kim SU, Kim S, Lee DS. Real-time in vivo monitoring of viable stem cells implanted on biocompatible scaffolds. *European journal of nuclear medicine and molecular imaging.* Apr 25 2008.

61. Ishii T, Asai T, Urakami T, Oku N. Accumulation of macromolecules in brain parenchyma in acute phase of cerebral infarction/reperfusion. *Brain research.* Mar 19 2010;1321:164-168.

62. Jackson H, Muhammad O, Daneshvar H, Nelms J, Popescu A, Vogelbaum MA, Bruchez M, Toms SA. Quantum dots are phagocytized by macrophages and colocalize with experimental gliomas. *Neurosurgery.* Mar 2007;60(3):524-529; discussion 529-530.

63. Jing W, Gershan JA, Johnson BD. Depletion of CD4 T cells enhances immunotherapy for neuroblastoma after syngeneic HSCT but compromises development of antitumor immune memory. *Blood.* Apr 30 2009;113(18):4449-4457.

64. Kadoch C, Dinca EB, Voicu R, Chen L, Nguyen D, Parikh S, Karrim J, Shuman MA, Lowell CA, Treseler PA, James CD, Rubenstein JL. Pathologic correlates of primary central nervous system lymphoma defined in an orthotopic xenograft model. *Clin Cancer Res.* Mar 15 2009;15(6):1989-1997.

65. Kadurugamuwa JL, Modi K, Coquoz O, Rice B, Smith S, Contag PR, Purchio T. Reduction of astrogliosis by early treatment of pneumococcal meningitis measured by simultaneous imaging, in vivo, of the pathogen and host response. *Infection and immunity.* Dec 2005;73(12):7836-7843.

66. Kadurugamuwa JL, Modi K, Yu J, Francis KP, Orihuela C, Tuomanen E, Purchio AF, Contag PR. Noninvasive monitoring of pneumococcal

meningitis and evaluation of treatment efficacy in an experimental mouse model. *Mol Imaging.* Apr-Jun 2005;4(2):137-142.

67. Kang SH, Cho HT, Devi S, Zhang Z, Escuin D, Liang Z, Mao H, Brat DJ, Olson JJ, Simons JW, Lavallee TM, Giannakakou P, Van Meir EG, Shim H. Antitumor effect of 2-methoxyestradiol in a rat orthotopic brain tumor model. *Cancer research.* Dec 15 2006;66(24):11991-11997.

68. Kang Y. Analysis of cancer stem cell metastasis in xenograft animal models. *Methods in molecular biology (Clifton, N.J.* 2009;568:7-19.

69. Keller AF, Gravel M, Kriz J. Live imaging of amyotrophic lateral sclerosis pathogenesis: disease onset is characterized by marked induction of GFAP in Schwann cells. *Glia.* Aug 1 2009;57(10):1130-1142.

70. Kelly EJ, Nace R, Barber GN, Russell SJ. Attenuation of vesicular stomatitis virus encephalitis through microRNA targeting. *Journal of virology.* Feb 2010;84(3):1550-1562.

71. Kemper EM, Leenders W, Kusters B, Lyons S, Buckle T, Heerschap A, Boogerd W, Beijnen JH, van Tellingen O. Development of luciferase tagged brain tumour models in mice for chemotherapy intervention studies. *European Journal of Cancer.* 2006;In Press, Corrected Proof.

72. Kievit FM, Omid V, Narayan B, Chen F, Jonathan WG, Donghoon L, Richard GE, James MO, Miqin Z. PEI-PEG-Chitosan-Copolymer-Coated Iron Oxide Nanoparticles for Safe Gene Delivery: Synthesis, Complexation, and Transfection. *Advanced Functional Materials.* 2009;19(14):2244-2251.

73. Kim SB, Ozawa T, Watanabe S, Umezawa Y. High-throughput sensing and noninvasive imaging of protein nuclear transport by using reconstitution of split Renilla luciferase. *Proceedings of the National Academy of Sciences of the United States of America.* August 2004;101(32):11542-11547.

74. Klein RL, Dayton RD, Tatom JB, Henderson KM, Henning PP. AAV8, 9, Rh10, Rh43 vector gene transfer in the rat brain: effects of serotype, promoter and purification method. *Mol Ther.* Jan 2008;16(1):89-96.

75. Ko MH, Kim S, Hwang do W, Ko HY, Kim YH, Lee DS. Bioimaging of the unbalanced expression of microRNA9 and microRNA9* during the neuronal differentiation of P19 cells. *The FEBS journal.* May 2008;275(10):2605-2616.

76. Kumagai G, Okada Y, Yamane J, Nagoshi N, Kitamura K, Mukaino M, Tsuji O, Fujiyoshi K, Katoh H, Okada S, Shibata S, Matsuzaki Y, Toh S, Toyama Y, Nakamura M, Okano H. Roles of ES cell-derived gliogenic neural stem/progenitor cells in functional recovery after spinal cord injury. *PLoS ONE.* 2009;4(11):e7706.

77. Lalancette-Hebert M, Moquin A, Choi AO, Kriz J, Maysinger D. Lipopolysaccharide-QD Micelles Induce Marked Induction of TLR2 and Lipid Droplet Accumulation in Olfactory Bulb Microglia. *Molecular pharmaceutics.* May 21 2010.

78. Lalancette-Hebert M, Phaneuf D, Soucy G, Weng YC, Kriz J. Live imaging of Toll-like receptor 2 response in cerebral ischaemia reveals a role of olfactory bulb microglia as modulators of inflammation. *Brain.* Jan 19 2009.

79. Lau YK, Murray LB, Houshmandi SS, Xu Y, Gutmann DH, Yu Q. Merlin is a potent inhibitor of glioma growth. *Cancer research.* Jul 15 2008;68(14):5733-5742.

80. Lauritzen KH, Moldestad O, Eide L, Carlsen H, Nesse G, Storm JF, Mansuy IM, Bergersen LH, Klungland A. Mitochondrial DNA toxicity in forebrain neurons causes apoptosis, neurodegeneration, and impaired behavior. *Molecular and cellular biology.* Mar 2010;30(6):1357-1367.

81. Lee JY, Kim S, Hwang DW, Jeong JM, Chung JK, Lee MC, Lee DS. Development of a Dual-Luciferase Reporter System for In Vivo Visualization of MicroRNA Biogenesis and Posttranscriptional Regulation. *J Nucl Med.* Feb 2008;49(2):285-294.

82. Leo BM, Li X, Balian G, Anderson DG. In vivo bioluminescent imaging of virus-mediated gene transfer and transduced cell transplantation in the intervertebral disc. *Spine.* April 2004;29(8):838-844.

83. Leucht P, Kim JB, Amasha R, James AW, Girod S, Helms JA. Embryonic origin and Hox status determine progenitor cell fate during adult bone regeneration. *Development (Cambridge, England).* Sep 2008;135(17):2845-2854.

84. Li JY, Wang H, May S, Song X, Fueyo J, Fuller GN, Wang H. Constitutive activation of c-Jun N-terminal kinase correlates with histologic grade and EGFR expression in diffuse gliomas. *Journal of neuro-oncology.* May 2008;88(1):11-17.

85. Lin AH, Luo J, Mondshein LH, ten Dijke P, Vivien D, Contag CH, Wyss-Coray T. Global Analysis of Smad2/3-Dependent TGF-{beta} Signaling in Living Mice Reveals Prominent Tissue-Specific Responses to Injury. *J Immunol.* July 2005;175(1):547-554.

86. Lipshutz GS, Gruber CA, Cao Y, Hardy J, Contag CH, Gaensler KM. In utero delivery of adeno-associated viral vectors: intraperitoneal gene transfer produces long-term expression. *Molecular Therapy.* March 2001;3(3):284-292.

87. Ljubimova JY, Fujita M, Khazenzon NM, Lee BS, Wachsmann-Hogiu S, Farkas DL, Black KL, Holler E. Nanoconjugate based on polymalic acid for tumor targeting. *Chemico-biological interactions.* Jan 30 2008;171(2):195-203.

88. Lobbestael E, Reumers V, Ibrahimi A, Paesen K, Thiry I, Gijsbers R, Van den Haute C, Debyser Z, Baekelandt V, Taymans JM. Immunohistochemical detection of transgene expression in the brain using small epitope tags. *BMC biotechnology.* 2010;10:16.

89. Luker GD, Bardill JP, Prior JL, Pica CM, Piwnica-Worms D, Leib DA. Noninvasive bioluminescence imaging of herpes simplex virus type 1

infection and therapy in living mice. *Journal of virology.* December 2002;76(23):12149-12161.

90. Luker KE, Hutchens M, Schultz T, Pekosz A, Luker GD. Bioluminescence imaging of vaccinia virus: Effects of interferon on viral replication and spread. *Virology.* Aug 8 2005.

91. Lun X, Alain T, Zemp FJ, Zhou H, Rahman MM, Hamilton MG, McFadden G, Bell J, Senger DL, Forsyth PA. Myxoma virus virotherapy for glioma in immunocompetent animal models: optimizing administration routes and synergy with rapamycin. *Cancer research.* Jan 15 2010;70(2):598-608.

92. Luo J, Ho P, Steinman L, Wyss-Coray T. Bioluminescence in vivo imaging of autoimmune encephalomyelitis predicts disease. *Journal of neuroinflammation.* 2008;5:6.

93. Luo J, Ho PP, Buckwalter MS, Hsu T, Lee LY, Zhang H, Kim DK, Kim SJ, Gambhir SS, Steinman L, Wyss-Coray T. Glia-dependent TGF-beta signaling, acting independently of the TH17 pathway, is critical for initiation of murine autoimmune encephalomyelitis. *J Clin Invest.* Nov 1 2007;117(11):3306-3315.

94. Ma MS, Van Dam G, Meek M, Boddeke E, Copray S. In vivo bioluminescent imaging of Schwann cells in a poly(DL-lactide-epsilon-caprolactone) nerve guide. *Muscle & nerve.* Jul 17 2009.

95. Maes W, Deroose C, Reumers V, Krylyshkina O, Gijsbers R, Baekelandt V, Ceuppens J, Debyser Z, Van Gool SW. In vivo bioluminescence imaging in an experimental mouse model for dendritic cell based immunotherapy against malignant glioma. *Journal of neuro-oncology.* Jan 2009;91(2):127-139.

96. Marian CO, Cho SK, McEllin BM, Maher EA, Hatanpaa KJ, Madden CJ, Mickey BE, Wright WE, Shay JW, Bachoo RM. The telomerase antagonist, imetelstat, efficiently targets glioblastoma tumor-initiating cells leading to decreased proliferation and tumor growth. *Clin Cancer Res.* Jan 1 2010;16(1):154-163.

97. Marques CP, Cheeran MC, Palmquist JM, Hu S, Urban SL, Lokensgard JR. Prolonged microglial cell activation and lymphocyte infiltration following experimental herpes encephalitis. *J Immunol.* Nov 1 2008;181(9):6417-6426.

98. Maysinger D, Behrendt M, Lalancette-Hebert M, Kriz J. Real-time imaging of astrocyte response to quantum dots: in vivo screening model system for biocompatibility of nanoparticles. *Nano Lett.* Aug 2007;7(8):2513-2520.

99. Melancon MP, Wang W, Wang Y, Shao R, Ji X, Gelovani JG, Li C. A novel method for imaging in vivo degradation of poly(l-glutamic Acid), a biodegradable drug carrier. *Pharm Res.* Jun 2007;24(6):1217-1224.

100. Michaud K, Solomon DA, Oermann E, Kim JS, Zhong WZ, Prados MD,

Ozawa T, James CD, Waldman T. Pharmacologic inhibition of cyclin-dependent kinases 4 and 6 arrests the growth of glioblastoma multiforme intracranial xenografts. *Cancer research.* Apr 15 2010;70(8):3228-3238.

101. Miretti S, Roato I, Taulli R, Ponzetto C, Cilli M, Olivero M, Di Renzo MF, Godio L, Albini A, Buracco P, Ferracini R. A mouse model of pulmonary metastasis from spontaneous osteosarcoma monitored in vivo by Luciferase imaging. *PLoS ONE.* 2008;3(3):e1828.

102. Moriyama EH, Bisland SK, Lilge L, Wilson BC. Bioluminescence imaging of the response of rat gliosarcoma to ALA-PpIX-mediated photodynamic therapy. *Photochemistry and photobiology.* Sep-October 2004;80(2):242-249.

103. Moriyama EH, Niedre MJ, Jarvi MT, Mocanu JD, Moriyama Y, Subarsky P, Li B, Lilge LD, Wilson BC. The influence of hypoxia on bioluminescence in luciferase-transfected gliosarcoma tumor cells in vitro. *Photochem Photobiol Sci.* Jun 2008;7(6):675-680.

104. Mukherjee B, McEllin B, Camacho CV, Tomimatsu N, Sirasanagandala S, Nannepaga S, Hatanpaa KJ, Mickey B, Madden C, Maher E, Boothman DA, Furnari F, Cavenee WK, Bachoo RM, Burma S. EGFRvIII and DNA double-strand break repair: a molecular mechanism for radioresistance in glioblastoma. *Cancer research.* May 15 2009;69(10):4252-4259.

105. Neff BA, Voss SG, Allen C, Schroeder MA, Driscoll CL, Link MJ, Galanis E, Sarkaria JN. Bioluminescent Imaging of Intracranial Vestibular Schwannoma Xenografts in NOD/SCID Mice. *Otol Neurotol.* Jan 2009;30(1):105-111.

106. Ohlfest JR, Demorest ZL, Motooka Y, Vengco I, Oh S, Chen E, Scappaticci FA, Saplis RJ, Ekker SC, Low WC. Combinatorial Antiangiogenic Gene Therapy by Nonviral Gene Transfer Using the Sleeping Beauty Transposon Causes Tumor Regression and Improves Survival in Mice Bearing Intracranial Human Glioblastoma. *Molecular Therapy.* 2005;12(5):778-788.

107. Ohlfest JR, Lobitz PD, Perkinson SG, Largaespada DA. Integration and long-term expression in xenografted human glioblastoma cells using a plasmid-based transposon system. *Mol Ther.* Aug 2004;10(2):260-268.

108. Okada S, Ishii K, Yamane J, Iwanami A, Ikegami T, Katoh H, Iwamoto Y, Nakamura M, Miyoshi H, Okano HJ, Contag CH, Toyama Y, Okano H. In vivo imaging of engrafted neural stem cells: its application in evaluating the optimal timing of transplantation for spinal cord injury. *Faseb J.* Sep 1 2005.

109. Orihuela CJ, Gao G, Francis KP, Yu J, Tuomanen EI. Tissue-specific contributions of pneumococcal virulence factors to pathogenesis. *J Infect Dis.* November 2004;190(9):1661-1669.

110. Orihuela CJ, Gao G, McGee M, Yu J, Francis KP, Tuomanen E.

Organ-specific models of Streptococcus pneumoniae disease. *Scand J Infect Dis.* 2003;35(9):647-652.

111. Ortiz-Abalia J, Sahun I, Altafaj X, Andreu N, Estivill X, Dierssen M, Fillat C. Targeting Dyrk1A with AAVshRNA attenuates motor alterations in TgDyrk1A, a mouse model of Down syndrome. *American journal of human genetics.* Oct 2008;83(4):479-488.

112. Otto-Duessel M, Khankaldyyan V, Gonzalez-Gomez I, Jensen MC, Laug WE, Rosol M. In vivo testing of Renilla luciferase substrate analogs in an orthotopic murine model of human glioblastoma. *Mol Imaging.* Apr-Jun 2006;5(2):57-64.

113. Pendharkar AV, Chua JY, Andres RH, Wang N, Gaeta X, Wang H, De A, Choi R, Chen S, Rutt BK, Gambhir SS, Guzman R. Biodistribution of neural stem cells after intravascular therapy for hypoxic-ischemia. *Stroke; a journal of cerebral circulation.* Sep 2010;41(9):2064-2070.

114. Peterson JR, Infanger DW, Braga VA, Zhang Y, Sharma RV, Engelhardt JF, Davisson RL. Longitudinal Non-invasive Monitoring of Transcription Factor Activation in Cardiovascular Regulatory Nuclei Using Bioluminescence Imaging. *Physiological genomics.* Jan 29 2008.

115. Porkka K, Koskenvesa P, Lundan T, Rimpilainen J, Mustjoki S, Smykla R, Wild R, Luo R, Arnan M, Brethon B, Eccersley L, Hjorth-Hansen H, Hoglund M, Klamova H, Knutsen H, Parikh S, Raffoux E, Gruber F, Brito-Babapulle F, Dombret H, Duarte RF, Elonen E, Paquette R, Zwaan CM, Lee FY. Dasatinib crosses the blood-brain barrier and is an efficient therapy for central nervous system Philadelphia chromosome-positive leukemia. *Blood.* Aug 15 2008;112(4):1005-1012.

116. Prins R, Bruhn KW, Craft N, Lin JW, Kim CH, Odesa SK, Miller JF, Liau LM. Central nervous system tumor immunity generated by a recombinant listeria monocytogenes vaccine targeting tyrosinase related protein-2 and real-time imaging of intracranial tumor burden. *Neurosurgery.* 2006;58(1):169-178.

117. Prins RM, Craft N, Bruhn KW, Khan-Farooqi H, Koya RC, Stripecke R, Miller JF, Liau LM. The TLR-7 agonist, imiquimod, enhances dendritic cell survival and promotes tumor antigen-specific T cell priming: relation to central nervous system antitumor immunity. *J Immunol.* Jan 1 2006;176(1):157-164.

118. Prins RM, Shu CJ, Radu CG, Vo DD, Khan-Farooqi H, Soto H, Yang MY, Lin MS, Shelly S, Witte ON, Ribas A, Liau LM. Anti-tumor activity and trafficking of self, tumor-specific T cells against tumors located in the brain. *Cancer Immunol Immunother.* Sep 2008;57(9):1279-1289.

119. Ragel BT, Elam IL, Gillespie DL, Flynn JR, Kelly DA, Mabey D, Feng H, Couldwell WT, Jensen RL. A novel model of intracranial meningioma in mice using luciferase-expressing meningioma cells. Laboratory investigation. *Journal of neurosurgery.* Feb 2008;108(2):304-310.

120. Randall LM, Amante FH, McSweeney KA, Zhou Y, Stanley AC, Haque A,

Jones MK, Hill GR, Boyle GM, Engwerda CR. Common strategies to prevent and modulate experimental cerebral malaria in mouse strains with different susceptibilities. *Infection and immunity.* Jul 2008;76(7):3312-3320.

121. Razmara M, Hilliard B, Ziarani AK, Murali R, Yellayi S, Ghazanfar M, Chen YH, Tykocinski ML. Fn14-TRAIL, a chimeric intercellular signal exchanger, attenuates experimental autoimmune encephalomyelitis. *The American journal of pathology.* Feb 2009;174(2):460-474.

122. Rehemtulla A, Hall DE, Stegman LD, Prasad U, Chen G, Bhojani MS, Chenevert TL, Ross BD. Molecular imaging of gene expression and efficacy following adenoviral-mediated brain tumor gene therapy. *Mol Imaging.* Jan-March 2002;1(1):43-55.

123. Reumers V, Deroose CM, Krylyshkina O, Nuyts J, Geraerts M, Mortelmans L, Gijsbers R, Van den Haute C, Debyser Z, Baekelandt V. Noninvasive and quantitative monitoring of adult neuronal stem cell migration in mouse brain using bioluminescence imaging. *Stem cells (Dayton, Ohio).* Sep 2008;26(9):2382-2390.

124. Rubin JB, Kung AL, Klein RS, Chan JA, Sun Y, Schmidt K, Kieran MW, Luster AD, Segal RA. A small-molecule antagonist of CXCR4 inhibits intracranial growth of primary brain tumors. *Proceedings of the National Academy of Sciences of the United States of America.* Nov 11 2003;100(23):13513-13518.

125. Ryman KD, Gardner CL, Burke CW, Meier KC, Thompson JM, Klimstra WB. Heparan sulfate binding can contribute to the neurovirulence of neuroadapted and nonneuroadapted Sindbis viruses. *Journal of virology.* Apr 2007;81(7):3563-3573.

126. Ryman KD, Gardner CL, Meier KC, Biron CA, Johnston RE, Klimstra WB. Early restriction of alphavirus replication and dissemination contributes to age-dependent attenuation of systemic hyperinflammatory disease. *J Gen Virol.* Feb 2007;88(Pt 2):518-529.

127. Sher F, van Dam G, Boddeke E, Copray S. Bioluminescence imaging of Olig2-neural stem cells reveals improved engraftment in a demyelination mouse model. *Stem cells (Dayton, Ohio).* Jul 2009;27(7):1582-1591.

128. Sims TL, Jr., Hamner JB, Bush RA, Williams RF, Zhou J, Kim SU, Aboody KS, Danks MK, Davidoff AM. Neural progenitor cell-mediated delivery of interferon beta improves neuroblastoma response to cyclophosphamide. *Annals of surgical oncology.* Nov 2008;15(11):3259-3267.

129. Spaccapelo R, Janse CJ, Caterbi S, Franke-Fayard B, Bonilla JA, Syphard LM, Di Cristina M, Dottorini T, Savarino A, Cassone A, Bistoni F, Waters AP, Dame JB, Crisanti A. Plasmepsin 4-deficient Plasmodium berghei are virulence attenuated and induce protective immunity against experimental malaria. *The American journal of pathology.* Jan

2010;176(1):205-217.

130. Stish BJ, Oh S, Vallera DA. Anti-glioblastoma effect of a recombinant bispecific cytotoxin cotargeting human IL-13 and EGF receptors in a mouse xenograft model. *Journal of neuro-oncology.* Mar 2008;87(1):51-61.

131. Sun A, Hou L, Prugpichailers T, Dunkel J, Kalani MA, Chen X, Kalani MY, Tse V. Firefly luciferase-based dynamic bioluminescence imaging: a noninvasive technique to assess tumor angiogenesis. *Neurosurgery.* Apr 2010;66(4):751-757; discussion 757.

132. Szentirmai O, Baker CH, Lin N, Szucs S, Takahashi M, Kiryu S, Kung AL, Mulligan RC, BS C. Noninvasive bioluminescence imaging of luciferase expressing intracranial U87 xenografts: correlation with magnetic resonance imaging determined tumor volume and longitudinal use in assessing tumor growth and antiangiogenic treatment effect. *Neurosurgery.* 2006;58(2):365-372.

133. Szentirmai O, Baker CH, Bullain SS, Lin N, Takahashi M, Folkman J, Mulligan RC, Carter BS. Successful inhibition of intracranial human glioblastoma multiforme xenograft growth via systemic adenoviral delivery of soluble endostatin and soluble vascular endothelial growth factor receptor-2: laboratory investigation. *Journal of neurosurgery.* May 2008;108(5):979-988.

134. Tamguney G, Francis KP, Giles K, Lemus A, Dearmond SJ, Prusiner SB. Measuring prions by bioluminescence imaging. *Proceedings of the National Academy of Sciences of the United States of America.* Aug 17 2009.

135. Taymans JM, Vandenberghe LH, Haute CV, Thiry I, Deroose CM, Mortelmans L, Wilson JM, Debyser Z, Baekelandt V. Comparative analysis of adeno-associated viral vector serotypes 1, 2, 5, 7, and 8 in mouse brain. *Human gene therapy.* Mar 2007;18(3):195-206.

136. VanHandel M, Alizadeh D, Zhang L, Kateb B, Bronikowski M, Manohara H, Badie B. Selective uptake of multi-walled carbon nanotubes by tumor macrophages in a murine glioma model. *Journal of neuroimmunology.* Mar 31 2009;208(1-2):3-9.

137. Veiseh M, Gabikian P, Bahrami SB, Veiseh O, Zhang M, Hackman RC, Ravanpay AC, Stroud MR, Kusuma Y, Hansen SJ, Kwok D, Munoz NM, Sze RW, Grady WM, Greenberg NM, Ellenbogen RG, Olson JM. Tumor paint: a chlorotoxin:Cy5.5 bioconjugate for intraoperative visualization of cancer foci. *Cancer research.* Jul 15 2007;67(14):6882-6888.

138. Vyas A, Kim SK, Giacomini N, Boothroyd JC, Sapolsky RM. Behavioral changes induced by Toxoplasma infection of rodents are highly specific to aversion of cat odors. *Proceedings of the National Academy of Sciences of the United States of America.* Apr 10 2007;104(15):6442-6447.

139. Wada M, Watanabe S, Chung UI, Higo N, Taniguchi T, Kitazawa S.

Noninvasive bioluminescence imaging of c-fos expression in the mouse barrel cortex. *Behavioural brain research.* Nov 30 2009.

140. Wallis de Vries BMJ-LH, Gooitzen M. van Dam, René A. Tio, Johannes S. de Jong, Riemer H.J.A. Slart, and Clark J. Zeebregts, N M. Multispectral Near-Infrared Fluorescence Molecular Imaging of Matrix Metalloproteinases in a Human Carotid Plaque Using a Matrix-Degrading Metalloproteinase–Sensitive Activatable Fluorescent Probe *Circulation.* 2009;119:534-536.

141. Wang F, Dennis JE, Awadallah A, Solchaga LA, Molter J, Kuang Y, Salem N, Lin Y, Tian H, Kolthammer JA, Kim Y, Love ZB, Gerson SL, Lee Z. Transcriptional Profiling of Human Mesenchymal Stem Cells Transduced with Reporter Genes for Imaging. *Physiological genomics.* Dec 30 2008.

142. Wang L, Martin DR, Baker HJ, Zinn KR, Kappes JC, Ding H, Gentry AS, Harper S, Snyder EY, Cox NR. Neural progenitor cell transplantation and imaging in a large animal model. *Neuroscience research.* Nov 2007;59(3):327-340.

143. Wiesner SM, Decker SA, Larson JD, Ericson K, Forster C, Gallardo JL, Long C, Demorest ZL, Zamora EA, Low WC, SantaCruz K, Largaespada DA, Ohlfest JR. De novo induction of genetically engineered brain tumors in mice using plasmid DNA. *Cancer research.* Jan 15 2009;69(2):431-439.

144. Wong HK, Lahdenranta J, Kamoun WS, Chan AW, McClatchey AI, Plotkin SR, Jain RK, di Tomaso E. Anti-vascular endothelial growth factor therapies as a novel therapeutic approach to treating neurofibromatosis-related tumors. *Cancer research.* May 1 2010;70(9):3483-3493.

145. Xiong Z, Gharagozlou S, Vengco I, Chen W, Ohlfest JR. Effective CpG immunotherapy of breast carcinoma prevents but fails to eradicate established brain metastasis. *Clin Cancer Res.* Sep 1 2008;14(17):5484-5493.

146. Yamaguchi S, Iikubo E, Hirose N, Kitajima T, Katagiri S, Kawamori A, Fujii-Taira I, Matsushima T, Homma KJ. Bioluminescence imaging of c-fos gene expression accompanying filial imprinting in the newly hatched chick brain. *Neuroscience research.* Feb 17 2010.

147. Yang L, Clarke MJ, Carlson BL, Mladek AC, Schroeder MA, Decker P, Wu W, Kitange GJ, Grogan PT, Goble JM, Uhm J, Galanis E, Giannini C, Lane HA, James CD, Sarkaria JN. PTEN loss does not predict for response to RAD001 (Everolimus) in a glioblastoma orthotopic xenograft test panel. *Clin Cancer Res.* Jun 15 2008;14(12):3993-4001.

148. Yin D, Ong JM, Hu J, Desmond JC, Kawamata N, Konda BM, Black KL, Koeffler HP. Suberoylanilide hydroxamic acid, a histone deacetylase inhibitor: effects on gene expression and growth of glioma cells in vitro and in vivo. *Clin Cancer Res.* Feb 1 2007;13(3):1045-1052.

149. Yoshimitsu M, Sato T, Tao K, Walia JS, Rasaiah VI, Sleep GT, Murray GJ, Poeppl AG, Underwood J, West L, Brady RO, Medin JA. Bioluminescent imaging of a marking transgene and correction of Fabry mice by neonatal injection of recombinant lentiviral vectors. *Proceedings of the National Academy of Sciences of the United States of America.* November 2004;101(48):16909-16914.

150. Yuan L, Siegel M, Choi K, Khosla C, Miller CR, Jackson EN, Piwnica-Worms D, Rich KM. Transglutaminase 2 inhibitor, KCC009, disrupts fibronectin assembly in the extracellular matrix and sensitizes orthotopic glioblastomas to chemotherapy. *Oncogene.* Nov 13 2006.

151. Yurek DM, Fletcher AM, Smith GM, Seroogy KB, Ziady AG, Molter J, Kowalczyk TH, Padegimas L, Cooper MJ. Long-term transgene expression in the central nervous system using DNA nanoparticles. *Mol Ther.* Apr 2009;17(4):641-650.

152. Zhang Y, Laterra J, Pomper MG. Hedgehog pathway inhibitor HhAntag691 is a potent inhibitor of ABCG2/BCRP and ABCB1/Pgp. *Neoplasia (New York, N.Y.* Jan 2009;11(1):96-101.

153. Zhao H, Tang C, Cui K, Ang BT, Wong ST. A screening platform for glioma growth and invasion using bioluminescence imaging. *Journal of neurosurgery.* Feb 6 2009.

154. Zhao H, Zhu J, Cui K, Xu X, O'Brien M, Wong KK, Kesari S, Xia W, Wong ST. Bioluminescence imaging reveals inhibition of tumor cell proliferation by Alzheimer's amyloid beta protein. *Cancer cell international.* 2009;9:15.

155. Zhu L, Ramboz S, Hewitt D, Boring L, Grass DS, Purchio AF. Non-invasive imaging of GFAP expression after neuronal damage in mice. *Neurosci Lett.* September 2004;367(2):210-212.