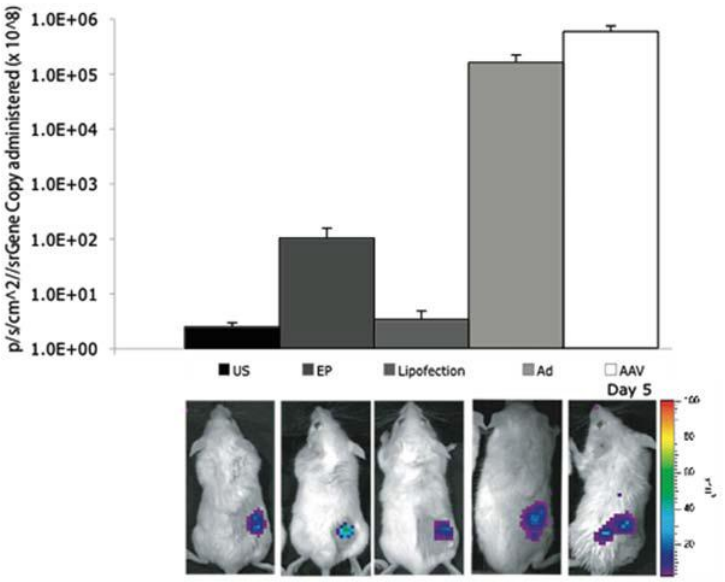
小动物活体光学成像技术在基因和细胞治疗中的应用

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，基因和细胞治疗是活体光学成像技术的热点之一。在活体光学成像实验中，常用于基因和细胞治疗的光学标记方法包括：1. 利用萤火虫荧光素酶（Firefly Luciferase）或者荧光蛋白作为报告基因，通过转基因技术标记细胞，病毒，细菌或者基因，进而观测基因和细胞治疗效果。2. 通过外源注射功能性荧光探针，观测基因和细胞治疗效果。

一．实时监测非侵入性基因送递和治疗

1. 不同载体的基因传递

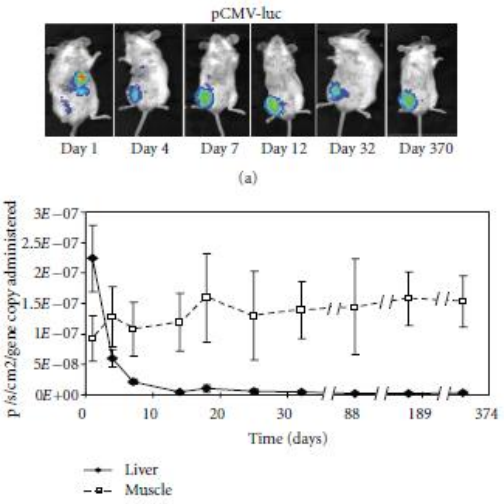
光学成像技术可以用来监测基因传递过程。进行转基因的载体包括病毒载体比如腺病毒 （Adenovirus，Ad），疱疹性口腔炎病毒 （Vesicular Stomatitis Virus, VSV）和单纯疱疹病毒（Herpes Simplex Virus, HSV）。其他的载体包括化学转染试剂比如脂质转染（Lipofection）和高分子聚合物（Polymer reagents）。下图所示，研究人员使用荧光虫荧光素酶标记的 pMVC-luc 质粒进行多种基因传递方式进行转染，如超声（US-Ultrasound），电穿孔（EP-Electroporation），脂质转染（Lipo-Lipofectamine 2000），腺病毒（Ad-Adenovirus 5）和腺相关病毒（AAV-Adeno-associated virus 2）转导。利用Revvity的 IVIS 成像系统可显示出腺病毒和腺相关病毒转导后所显示生物发光最强，说明这两种方法的效率最高。



(Tangney and Francis, Current Gene Therapy, 2012)

上图：在小鼠皮下 JBS 纤维肉瘤移植后，使用超声，电穿孔，脂质转染，腺病毒和腺相关病毒转导进行质粒基因传递。

研究人员使用电穿孔的方法在小鼠的不同部位如肝脏和肌肉部位进行萤火虫荧光素酶标记的 pMVC-luc 质粒转染，利用 Revvity的 IVIS 成像系统观测转染后的生物发光强度，发现质粒在肌肉中的转染效率更高（下图）。

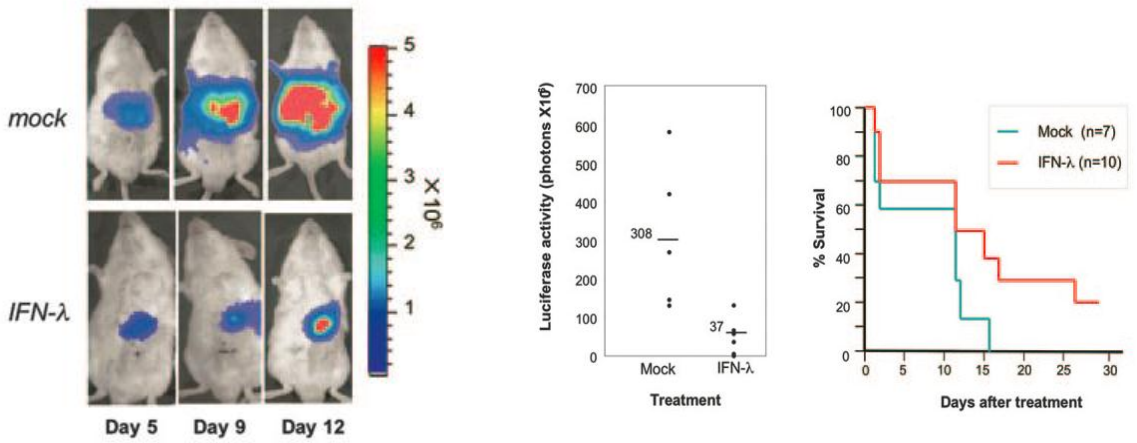


pMVC-luc 质粒转导到小鼠的肝脏和肌肉部位后，观测体内的生物发光强度。

（Morrisey et al, J Biomed Biotech, 2012）

2. 传递 DNA 治疗疾病

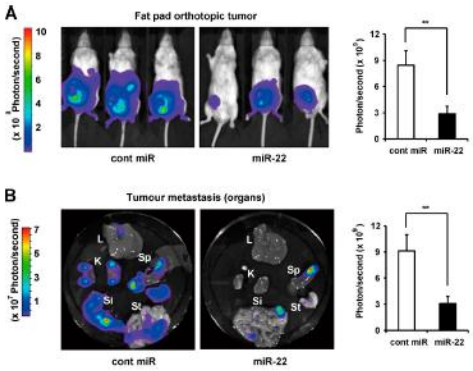
基因传递细胞因子基因比如 IFN 质粒能够调节天生免疫系统和适应性免疫系统。研究人员在回结肠动脉注射萤火虫荧光素标记结肠癌细胞株（luc-Conlon26 cell）使肿瘤转移到肝脏，然后静脉注射 IFN-λ 质粒。Revvity的 IVIS 系统成像结果显示注射 IFN-λ 质粒的小鼠结肠癌生物发光强度明显下降，而且结肠癌小鼠的存活率明显提高。这说明 IFN-λ质粒传递能够显著的阻止结肠肿瘤细胞的生长，从而帮助治疗人类恶性肿瘤（下图）。



（Sato et al, J. Immunology, 2006)

3. 使用 RNA 治疗疾病

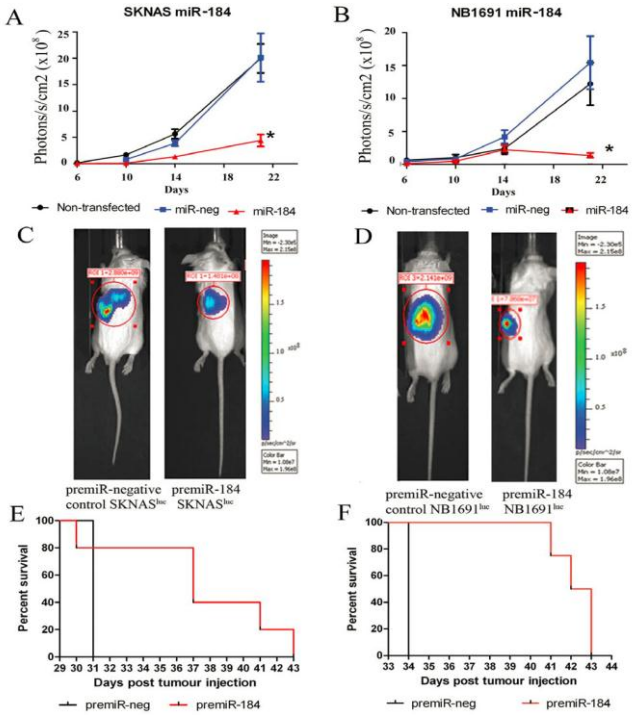
细胞衰老在癌症的发展中起到了重要作用， microRNAs 可以调节细胞衰老。研究人员在萤火虫荧光素酶标记 MDA-MB-231-luc 乳腺癌细胞建立的肿瘤模型中，注射 microRNA （衰老相关 miR22）。Revvity的 IVIS 成像系统结果显示 miR-22 在小鼠体内能够通过诱导细胞衰老从而抑制肿瘤的生长和转移（下图）。



在小鼠乳腺癌部位注射 miR-22, 46 天后，小鼠体内的乳腺癌细胞生物发光强度明显下降（A）。取出不同器官包括肝脏 (L， Liver)，肾脏（K， Kidney），脾脏（Sp，Spleen），胃（St， Stomach）和小肠（SI, Small Intestine）。这些器官的生物发光强度也明显下降（B）。

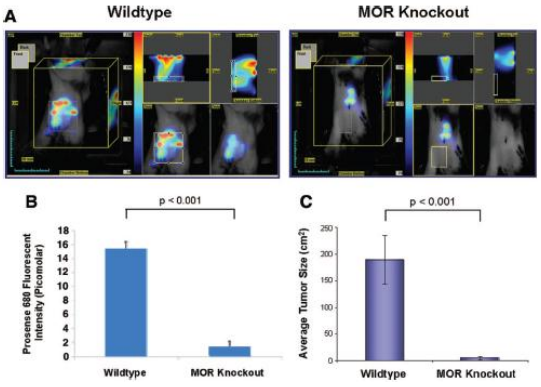
（Xu et al, J Cell Biol, 2011 ）

神经细胞瘤是从交感神经系统的前体细胞引发的癌症。在 In vitro 研究中，micro RNA（miR-184）能够抑制神经细胞瘤细胞在细胞培养液中的生长。因此，研究 miR-184 在活体中的作用是非常有意义的。研究人员在小鼠腹膜后注射 miR-184 高表达的萤火虫荧光素标记人神经细胞瘤细胞（SKN-AS^{luc} or NB1691^{luc}），Revvity的 IVIS 成像系统结果显示 miR-184 能够抑制神经细胞瘤细胞的发光强度，而且提高肿瘤小鼠的存活率（下图）。研究结果说明 miR-184 能够抑制神经细胞瘤细胞在原位异种移植瘤模型内的增殖，应用 miR-184 是治疗神经胶质瘤的潜在疗法。



（Tivnan et al, BMC Cancer, 2011 ）

shRNA（short hairpin RNA）能够用来干扰 RNA 使基因沉默。研究人员使用 shRNA 敲除阿片受体基因的肺癌小鼠，注射 Revvity公司的 Prosensen680 探针探测肿瘤的组织蛋白酶活性从而了解 shRNA 对于肺癌小鼠的治疗效果。使用 Revvity公司的FMT 小动物活体荧光断层成像系统观测 Prosense680 荧光强度，结果显示使用 shRNA 敲除阿片受体基因能够明显的抑制组织蛋白酶活性和肺癌肿瘤细胞的生成（下图）。

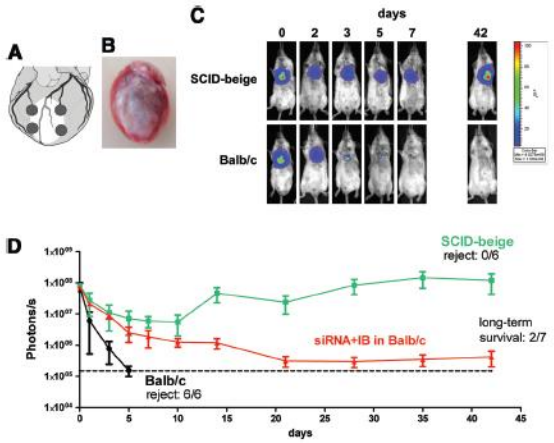


使用野生型 (Wildtype)和 shRNA 敲除阿片受体基因 (MOR Knockout) 的小鼠皮下移植荧光蛋白（GFP /RFP ）标记的 Lewis 肺癌细胞（Lewis lung carcinoma, LLC）。尾静脉注射 Prosense680，使用 FMT 观测和定量荧光强度（A&B），图像分析肿瘤细胞（C）。

（Mathew et al, Int Anaesthia Res, 2011 ）

二．细胞治疗

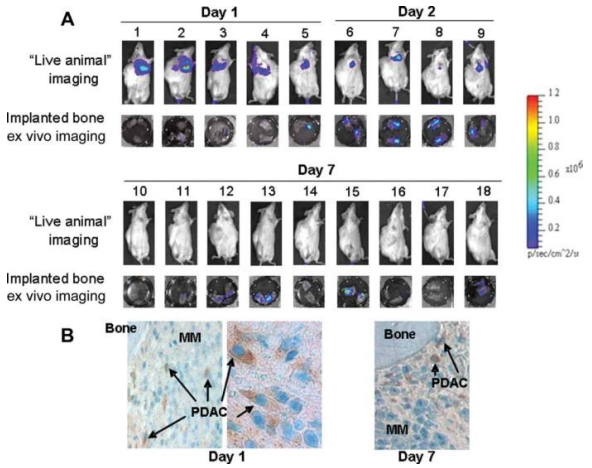
人类胚胎干细胞能够运用于细胞移植治疗，然而在细胞移植后会发生免疫排斥反应，因此研究低抗原性的胚胎干细胞并且提高移植后细胞活性是干细胞移植应用的热点。研究人员移植萤火虫荧光素酶标记人白细胞抗原敲除的胚胎干细胞到具有免疫活性的急性心肌梗塞小鼠模型，免疫排斥反应减轻而且胚胎干细胞的存活率提高 （下图）。结果说明敲除白细胞抗原的胚胎干细胞能够激发 T 细胞忽视和减轻异种免疫排斥，低抗原性的胚胎干细胞能够提高移植后细胞的活性。



（A&B）注射人胚胎干细胞到小鼠心脏梗塞部位（C）使用 Revvity公司的 IVIS 系统成像显示胚胎干细胞在免疫缺陷小鼠（SCID-beige）中的生物发光时间明显长于具有免疫活性（Balb /c）的小鼠（D）敲除人白细胞抗原的胚胎干细胞（siRNA+IB）在免疫缺陷小鼠（SCID-beige）的存活时间明显提高，减低了免疫排斥反应。

（Deuse et al, Circulation, 2011 ）

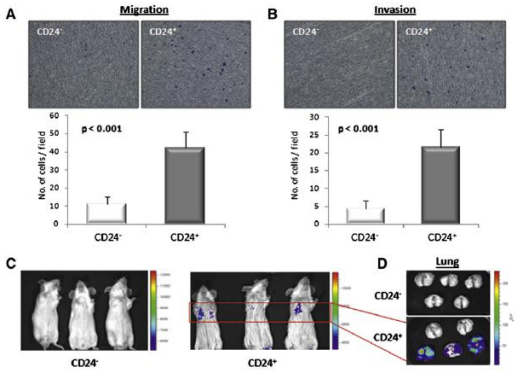
人体胚胎素在间充质干细胞和造血干细胞的细胞治疗中有非常重要的作用，包括提高造血干细胞的移植成活率，炎症调节，骨修复和癌症。人胚胎源贴壁细胞是从人产后胚胎分离出的间充质样干细胞。研究人员骨内移植 H929 骨髓瘤细胞到严重联合免疫缺陷（SCID）小鼠，静脉注射萤火虫荧光素酶和增强型绿色荧光蛋白（EGFP）标记人胚胎源贴壁细胞，Revvity的 IVIS 系统显示人胚胎源贴壁细胞能够位移到骨髓瘤骨内从而促进细胞生长（下图）。



静脉注射萤火虫荧光素酶和增强型绿色荧光蛋白标记人胚胎贴壁细胞到骨髓瘤小鼠模型（A）探测人胚胎贴壁细胞在小鼠体内生物发光强度 (B) 使用组织切片样品，免疫组化监测绿色荧光蛋白（GFP）发光强度。

（Li et al, Stem Cells, 2011）

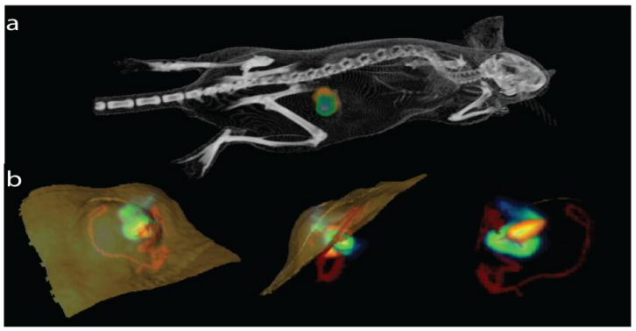
肝癌是全球第五大癌症，治疗肝癌的首选方法是肝脏移植或者手术切除。肿瘤晚期病人手术切除治疗后有高复发率，因此使用化学疗法是治疗晚期肿瘤患者的第二选择。然而总体来说治疗效果并不理想，主要原因是肿瘤细胞的高化疗抗性和化疗治疗剂本身的毒性，因此研究肝癌的化疗抗性对提高治疗的效率和患者康复有重要作用。研究发现肿瘤干细胞对化学治疗有强的抵抗力，因此肿瘤干细胞对肿瘤在常规治疗后的复发起关键作用。研究者使用异种移植化疗抗性肝癌小鼠，顺铂（cisplatin）化学治疗后, CD24（一种粘蛋白样细胞表面糖蛋白）表达上调。因此为了研究 CD24 在肿瘤干细胞高化疗抗性的作用，静脉注射 $CD24^+$人肝癌细胞到免疫缺陷/非肥胖糖尿病（NOD/SCID）小鼠，Revvity的 IVIS 系统成像显示肿瘤在小鼠体内形成，而且能够自我维持，分化和转移，然而敲除 CD24 的人肝癌细胞抑制肿瘤干细胞形态形成（下图）。结果说明 CD24 信号通路是肝癌患者的治疗靶位。



（A&B）*In vitro* 肿瘤细胞迁移和侵袭实验，$CD24^+$人肝癌细胞相对于 CD^-人肝癌细胞显示更高的移动和侵入效率。小鼠活体内（C）和肝脏组织（D）生物发光成像显示，注射 $CD24^+$人肝癌细胞的小鼠形成肿瘤的比率高。

（Lee et al, Cell, 2011 ）

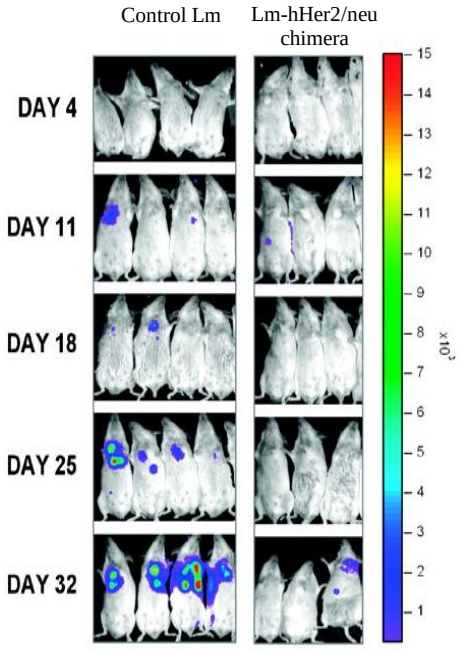
使用细菌能够用于实时监测传染性疾病和基因治疗研究的效果。皮下注射萤火虫荧光素酶标记结肠癌细胞株（HCT 116）形成肿瘤小鼠模型，然后尾静脉注射细菌荧光素酶标记的 *B.breve* UCC2003。Revvity的 IVIS 系统三维成像显示细菌荧光素酶标记*B. breve* 和生物发光标记 HCT116 共定位（下图）。结果说明使用非病原性细菌可以作为载体用于癌症靶位治疗。



(a) 小鼠体内的多模式成像：标记细菌（*B.breve*）生物发光，结肠癌细胞(HCT116) 生物发光和 μCT 成像。（细菌生物发光：橘色, 细胞癌生物发光：绿色）。（b）小鼠皮下肿瘤内放大成像。活肿瘤细胞（绿色/ 蓝色），脉管系统（造影剂-红色）和细菌（橘色 / 黄色）。

（Cronin et al, Plos, 2012 ）

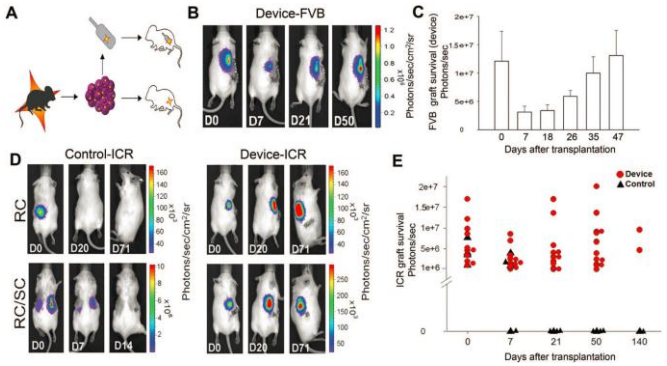
人表皮生长因子受体 2（HER2）的高表达，点突变和基因删除是和多种癌症（乳腺癌，卵巢癌，胰脏癌，胃癌和直肠癌）紧密相联系的。单核细胞增多性李斯特菌（Lm，Listeria monocytogenes）是一种兼性胞内寄生菌，而且可以用于疫苗载体。给予 Balb /c 小鼠新型单核细胞增多性李斯特菌-人表皮生长因子受体 2 嵌合疫苗免疫注射，然后静脉注射萤火虫荧光素标记小鼠乳腺癌细胞（4T1-luc）。Revvity的 IVIS 系统成像显示嵌合疫苗免疫乳腺癌肿瘤小鼠的生物发光强度明显弱于单核细胞增多性李斯特菌免疫的对照组（下图）。结果说明细菌受体嵌合疫苗能够明显推迟肺癌肿瘤负载，转移和提高小鼠存活率。



Balb/c 小鼠免疫单核细胞增多性李斯特菌（control Lm），或者单核细胞增多性李斯特菌-人表皮生长因子受体 2 嵌合疫苗（Lm-hHer2/neu chimera）。然后静脉注射萤火虫荧光素标记小鼠乳腺癌细胞（4T1-luc）。

（Seavey et al, Clin. Cancer Res，2009)

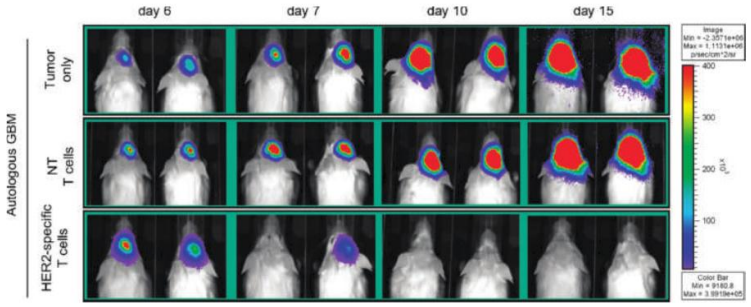
利用胰岛细胞移植治疗一型糖尿病的障碍是患者慢性免疫抑制的问题。然而服用免疫抑制药物不仅能够增加传染性疾病和恶性肿瘤发病率而且产生 β 细胞再生的紊乱。研究如何包膜细胞进行移植，降低和消除移植中的免疫抑制是现在研究的热点。研究者使用 TheraCyte 大包囊技术包裹萤火虫荧光素酶标记 β 细胞进行移植，Revvity的 IVIS 系统成像显示 TheraCyte 大包囊包膜的 β 细胞在异种移植的小鼠中生物发光强度提高，结果说明 TheraCyte 大包囊能够提高异种移植的 β 细胞成活率（下图）。利用 TheraCyte 大包囊技术可以进行细胞治疗糖尿病。



(Lee *et al*, Transplantation, 2009)

上图：（A）实验原理的示意图。（B）萤火虫荧光素酶标记的新生 FVB 小鼠胰岛细胞包膜，移植到 wtFVB 小鼠。（C）生物发光定量分析结果。（D）无包膜的 FVB 小鼠胰岛细胞通过肾脏间室（Renal compartment，RC）或者皮下（contra-lateral subcutaneous，RC/SC）注射移植到 ICR 小鼠 （Control-ICR）。TheraCyte 大包囊包膜的 FVB 小鼠胰岛细胞异种移植到 ICR 小鼠 (Device-ICR)。（E）生物发光定量分析利用 TheraCyte 大包囊技术进行移植和对照结果。

多形性成胶质细胞瘤是最具有侵越性的原发性脑瘤。目前来说，手术切除结合放射和化学疗法是治疗多形性成胶质细胞瘤的最好方法。然而对于中老年患者，放射和化学治疗只能减缓而不能阻止肿瘤细胞生长。CD133+肿瘤干细胞的化学和放射疗法耐药性能够解释传统疗法低效率的原因。正位异种移植萤火虫荧光素酶标记的人多形性成胶质细胞瘤细胞到免疫缺陷小鼠（SCID）前额叶，建立多形性成胶质细胞瘤小鼠模型。肿瘤内注射 HER2 靶向的嵌合性 T 细胞，Revvity的 IVIS 系统成像显示经过特异性 HER2+ T 细胞治疗小鼠的生物发光明显下降（下图）。结果说明特异性 HER2+ T 细胞能够抑制多形性成胶质细胞瘤的生长，从而进行有效治疗多形性成胶质细胞瘤患者。



(Ahmed *et al*, Clinical Cancer Research, 2010)

上图：首行（没有治疗的多形性成胶质细胞瘤小鼠）中行（T 细胞治疗多形性成胶质细胞瘤小鼠）末行（特异性 HER2+ T 细胞治疗多形性成胶质细胞瘤小鼠）。

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