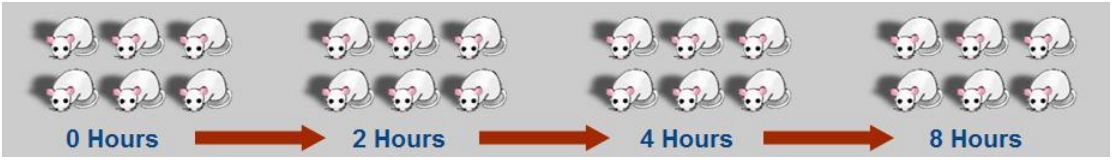
小动物活体光学成像技术在肿瘤研究中的应用

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，肿瘤研究是目前应用最为普遍的领域之一。常用于肿瘤活体成像的光学标记方法包括：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标记肿瘤细胞而直接观测肿瘤的发展变化，或标记特定基因而研究肿瘤相关基因在肿瘤发展中的作用；2、通过外源注射功能性荧光探针，观测肿瘤发展过程中的分子事件，进而反映肿瘤的发展变化。宏观来说，应用小动物活体光学成像技术进行肿瘤研究主要集中于三个方面：1、长时间监测肿瘤生长及转移；2、抗肿瘤药物研发；3、癌症分子机理研究。下面结合一些具体实例进行阐述：

一.长时间监测肿瘤生长及转移

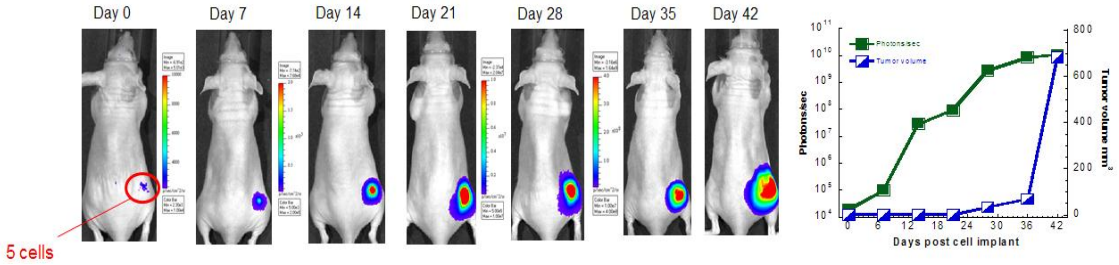
随着肿瘤研究的深入，应用传统方法（如卡尺测量肿瘤体积、肿瘤组织切片等）进行肿瘤研究已存在诸多限制。如进行组织切片观测前需要处死小鼠取出肿瘤组织，因此，在不同时间点或不同实验组都需要处死一批实验小鼠以获取足够的统计学数据，这样不但大大增加了实验成本，而且很难消除由于小鼠个体差异而产生的误差，无法获取可靠的重复性数据，同时，在制作切片时也无法保证实验的准确性，而利用活体光学成像技术可以对同一批小鼠进行不同时间点的长时间观测，进而大幅降低实验成本，并获取重复可靠的实验数据；

传统方法=6 只小鼠/时间点，4 个观测点共 24 只小鼠

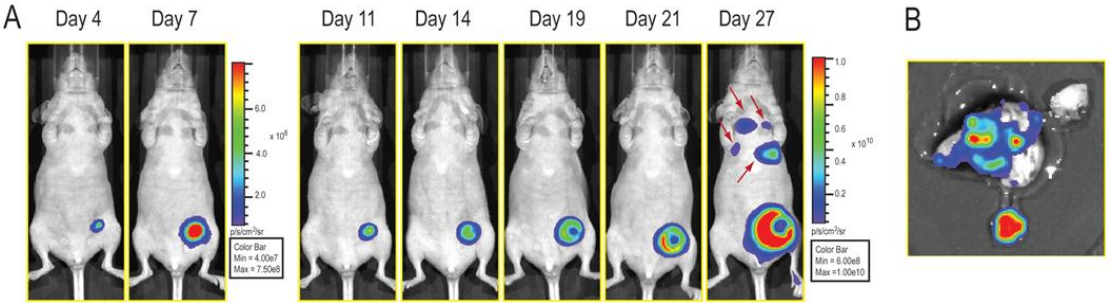


活体光学成像方法=对同一组 6 只小鼠进行 4 个不同时间点连续观测，共 6 只小鼠

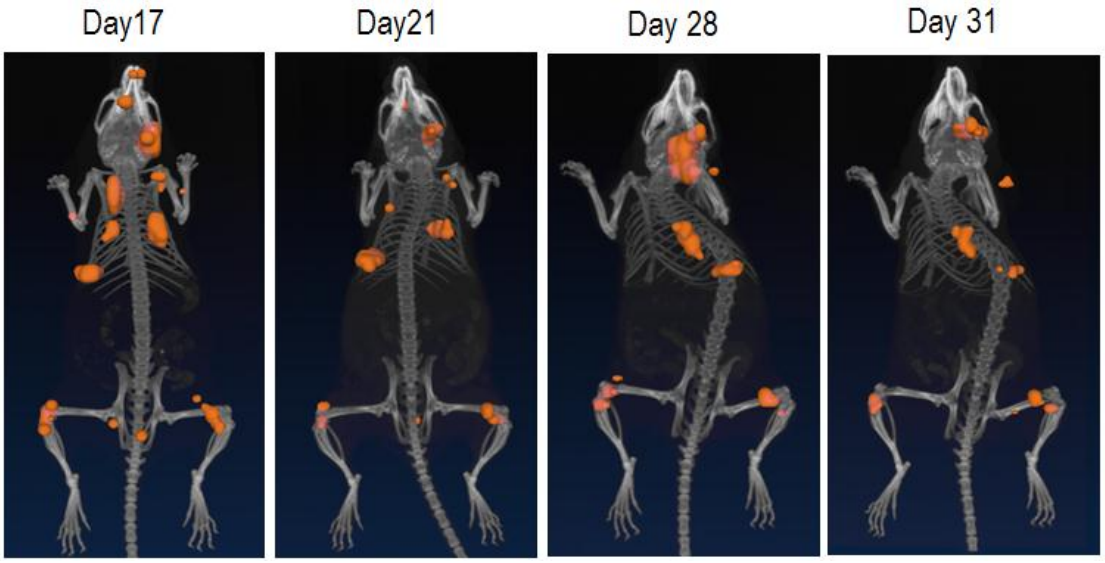
又如通过利用卡尺测量肿瘤体积的方法，只能等肿瘤发展至可以测量的程度才能开展实验，因此，无法进行肿瘤早期观测及微小转移灶的观测，而利用灵敏的生物发光成像技术在肿瘤发生早期即可进行有效观测，从而对肿瘤的整个发展过程进行全程监测，有力弥补了传统方法的缺陷。下面几个例子展示了应用生物发光成像技术长时间监测肿瘤的生长及转移。



上图：利用萤火虫荧光素酶标记 4T1 乳腺癌细胞建立皮下肿瘤模型，通过 IVIS 成像系统长期监测肿瘤的生长情况，在肿瘤细胞皮下注射的当天即可灵敏的观测到由 5 个被标记肿瘤细胞发出的光信号。定量分析显示，利用传统卡尺测量的方式（蓝色曲线）到 30 天左右才能明显看出肿瘤生长的差异，而利用生物发光成像技术（绿色曲线）在细胞皮下注射 7 天即可观测到肿瘤的生长，并对随后的发展变化进行长期观测。



上图：A.利用萤火虫荧光素酶标记 MDA-MB-231 乳腺癌细胞建立原位乳腺癌模型，通过 IVIS 成像系统长期监测肿瘤的生长情况，在注射后 27 天观测到其他部位的转移信号。B.体外组织成像进一步验证转移的发生。



上图：应用 IVIS 成像系统进行肿瘤信号的 3D 光学成像（橙色），同时应用 Quantum FX uCT 成像系统进行 3D 解剖学成像（骨架），并将 3D 光学功能性结果与 3D 解剖学结果进行影像融合，而确定肿瘤的骨转移。

二.抗肿瘤药物研发

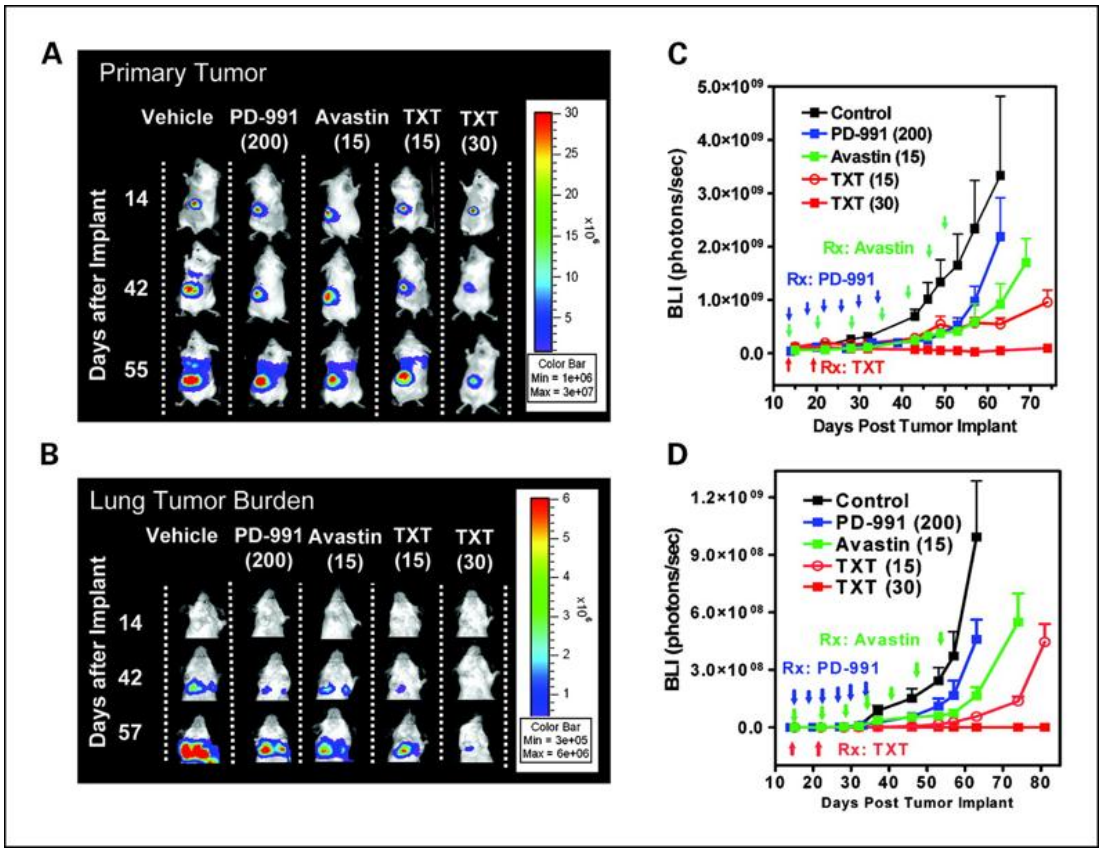
Revvity的小动物活体光学成像技术已广泛应用于肿瘤治疗药物的临床前研发阶段，发挥越来越重要的作用。全球各大制药企业均已采用活体光学成像技术开展抗肿瘤新药的研发，其中已有 6 种药物获得 FDA 认证，另有 8 种药物处于临床测试阶段。

FDA Approved Drugs	Drugs currently in clinical trials
▪ Sutent (Pfizer): subcutaneous tumer xenograft	▪ ABT-888 (Abbott): multiple diverse tumor models
▪ Dasatinib (Bristol-Myers Squibb): chronic myelogenous leukemia	▪ RANKL Inhibitor (Amgen): denosumab and bone metastasis models
▪ Tasigna (Novartis): leukemia/metastasis model	▪ Panzem (EntreMed Pharmaceuticals): orthotopic gliosarcoma
▪ Cubicin (Cubist Pharmaceuticals): bacterial peritonitis model	▪ AEE788 (Novartis): intraperitoneal tumor model
▪ Aflibercept (Sanofi-Aventis): orthotopic renal cancer	▪ IT-101/CRLX 101 (Insert Therapeutics, Cerulean Pharma Inc.): Ewings sarcoma
▪ Velcade (Millennium Pharmaceuticals): multiple myeloma	▪ CHIR-258 (Novartis): orthotopic multiple myeloma model
	▪ NPI-0052 (Nereus Pharmaceuticals): subcutaneous tumor model
	▪ CG0070 (Cell Genesys): orthotopic bladder cancer (*status of trial unknown)

应用小动物活体光学成像技术进行新药研发，主要包括以下方面：1、在活体动物水平进行药效评价；2、观测药物在活体动物体内的靶向、分布及代谢。

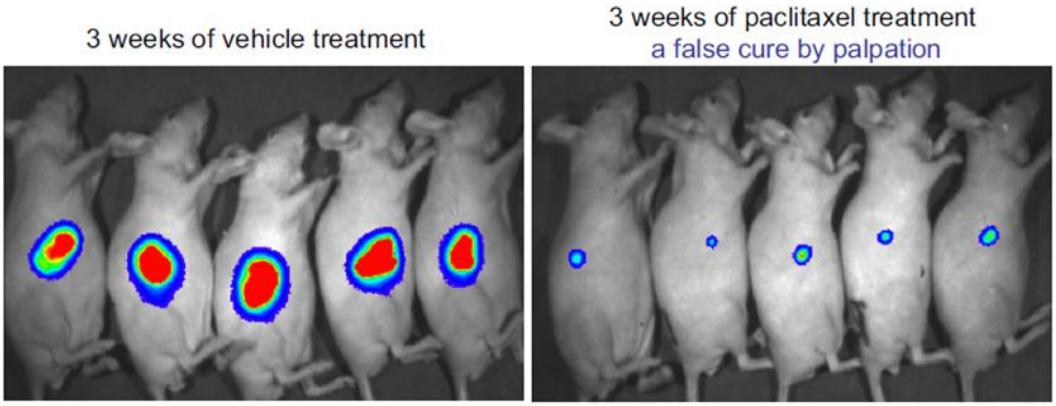
1、 药效评价

利用荧光素酶标记肿瘤细胞，并移植入动物体内建立肿瘤疾病动物模型，应用小动物活体光学成像技术观测给药后肿瘤光学信号的变化情况，进而评价不同药物、特定的给药途径、时间、剂量等给药策略对于肿瘤的治疗效果，如下图：



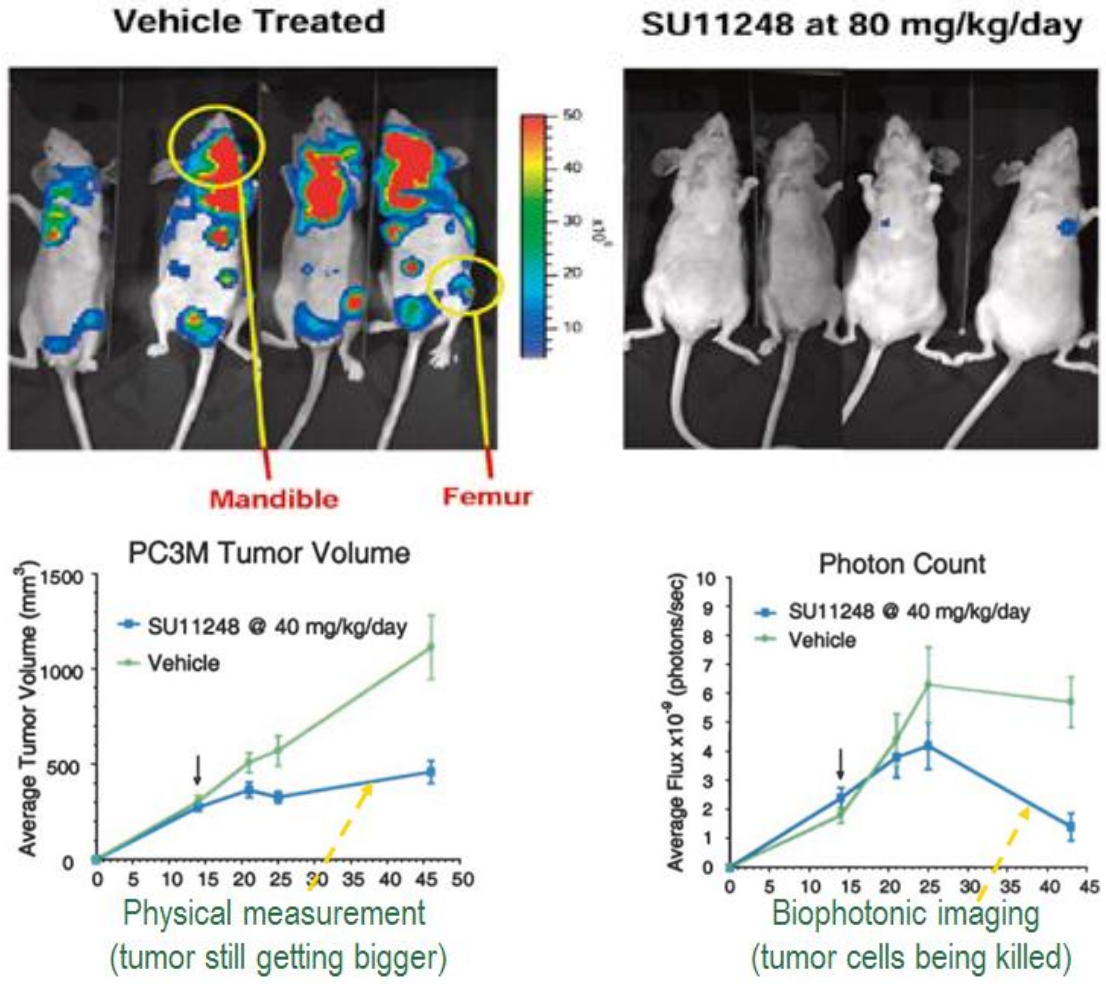
药效评价研究：利用萤火虫荧光素酶标记 MDA-MB-435 乳腺癌细胞株，将细胞注入小鼠肾包膜下构建肾包膜肿瘤模型，进而对 3 种不同药物或不同剂量的治疗效果进行评价。（A,C）应用 IVIS 成像系统长期观测 3 种药物对肾包膜乳腺癌移植瘤的治疗效果，并进行定量分析，结果显示 30 mg/kg Docetaxel（TXT）对肿瘤的生长抑制效果最好；（B,D）应用 IVIS 成像系统长期观测 3 种药物对肾包膜乳腺癌移植瘤肺部转移的抑制效果，并进行定量分析，结果显示 30 mg/kg Docetaxel（TXT）对肿瘤转移的抑制效果最好。

相对于触诊、肿瘤体积测量等传统方法，利用高灵敏度的生物发光成像技术进行药物评价，可以更灵敏的发现残余病灶点或尽早发现肿瘤的复发，从而更准确的对药物治疗效果进行判定，如下例：

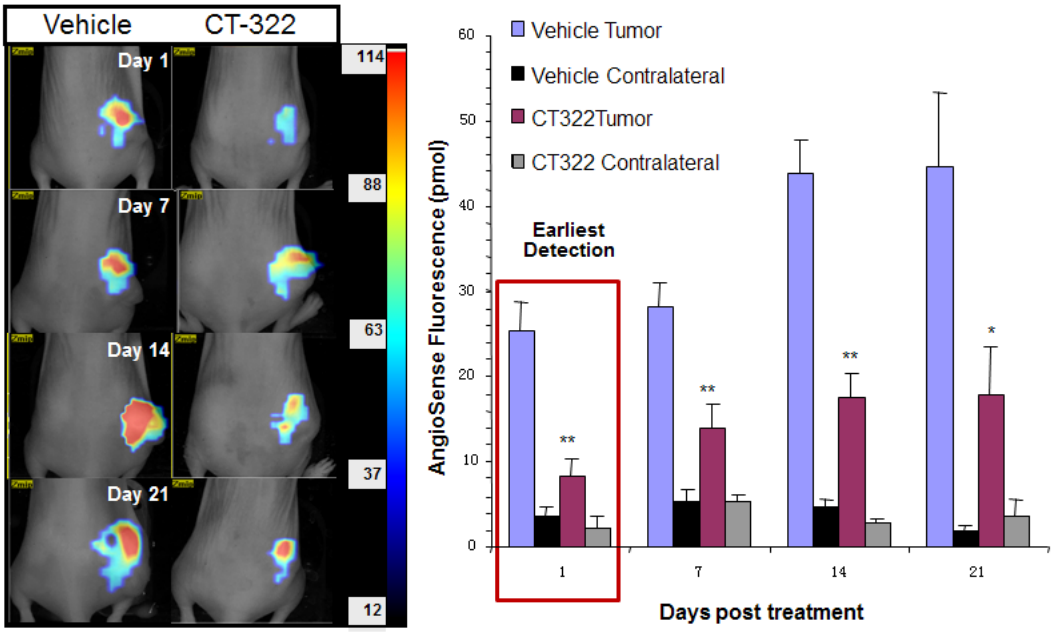


提高药效评价准确性：利用萤火虫荧光素酶标记 PC-3M 人前列腺肿瘤细胞株，建立肿瘤皮下移植模型进行药物评价。左图：对照组，右图：治疗组。通过高灵敏度的生物发光成像技术可以准确检测出药物治疗后的残余病灶点，从而进行正确的药效评价，而如果通过触诊等传统方法则可能做出错误判断。

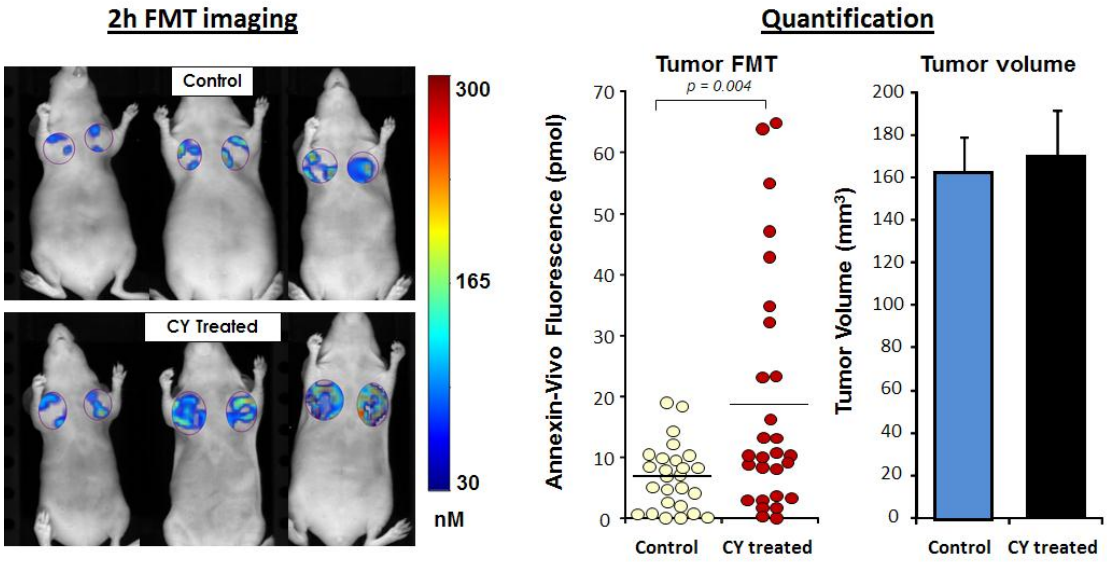
利用生物发光成像技术进行药效评价的另一独特优势在于，可以明确判断药物是否有效杀死肿瘤活细胞。这是由于生物发光的原理是基于活细胞环境的酶促反应，因此，能够发光的细胞必定是具有活性的。下图所示为辉瑞公司抗肿瘤药物 Sutent 的部分研究结果，研究人员首先利用卡尺测量肿瘤体积的方法观测该药物对于肿瘤的生长抑制情况，发现该药物能够延缓肿瘤的生长，但体积测量数据显示肿瘤并未变小，研究人员随后利用生物发光成像技术进行观测，发现给药一定时间后肿瘤光学信号显著降低，说明该药物对肿瘤活性细胞确实具有杀伤作用，同时说明单独依靠肿瘤体积测量的方式无法准确真实反映药物治疗效果。凭借活体光学成像的实验结果，Sutent 得以顺利通过 FDA 的认证。



除了应用生物发光技术研究药物对于肿瘤的治疗效果之外，荧光成像技术同样可以应用于此类研究，主要方式为通过外源注射功能性荧光试剂观测药物对于肿瘤某一方面的治疗情况，如利用反映血管生成的荧光试剂观测药物对于肿瘤血管新生的抑制情况，又如利用反映细胞凋亡的荧光试剂观测由于药物治疗而诱发的肿瘤细胞凋亡情况。



上图：应用 FMT 荧光断层成像系统结合 AngioSense750 荧光试剂研究 CT322 药物在抑制肿瘤血管新生方面的作用效果，结果表明 CT322 可以通过抑制肿瘤血管新生进而抑制肿瘤的生长。



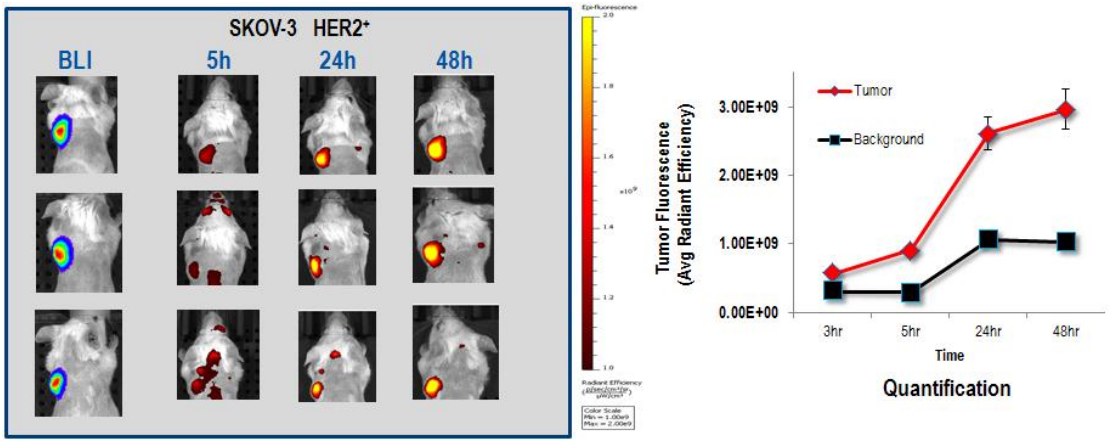
上图：应用 FMT 荧光断层成像系统结合 Annexin-Vivo 750 荧光试剂观测药物处理后引发的肿瘤细胞凋亡，定量结果显示应用荧光成像技术能够灵敏观测到药物诱导的细胞凋亡发生，而肿瘤体积测量数据显示对照组和治疗组的肿瘤体积无明显差异，因而无法反映药物诱导的细胞凋亡情况。

2、观测药物靶向、分布及代谢

除了在药效学中的应用，小动物活体光学成像也广泛应用于药物在体内靶向、分布及代谢的研究。与药效学中的应用不同，此类应用是以药物为直接观测对象，因此标记方式通常是利用荧光探针直接标记药物本身，通过追踪荧光信号而反映药物在体内的分布情况。

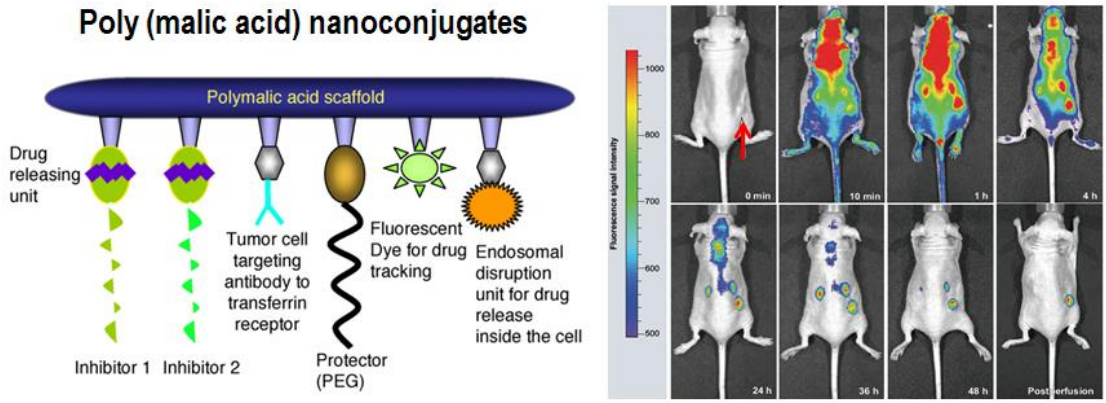
例如在研究抗体或多肽类药物是否能够有效靶向肿瘤的实验中，可以利用荧光染料

通过化学键的结合标记目标抗体或多肽，经尾静脉注射后，利用小动物活体光学成像系统观测上述标记对象的肿瘤靶向性，如下图：



药物的肿瘤靶向性研究：利用 VivoTag 645 荧光染料标记抗癌药物曲妥珠单抗(Trastuzumab)，尾静脉注入携带 HER2 阳性人卵巢癌 SKOV3 的 SCID 小鼠体内，通过荧光成像观测不同时间点药物对肿瘤的靶向情况（左上图后三列），肿瘤本身已被荧光素酶标记而通过生物发光成像（左上图最左列），右上图为荧光定量分析结果，标明曲妥珠单抗对 HER2 阳性的人卵巢癌 SKOV3 具有良好靶向性。

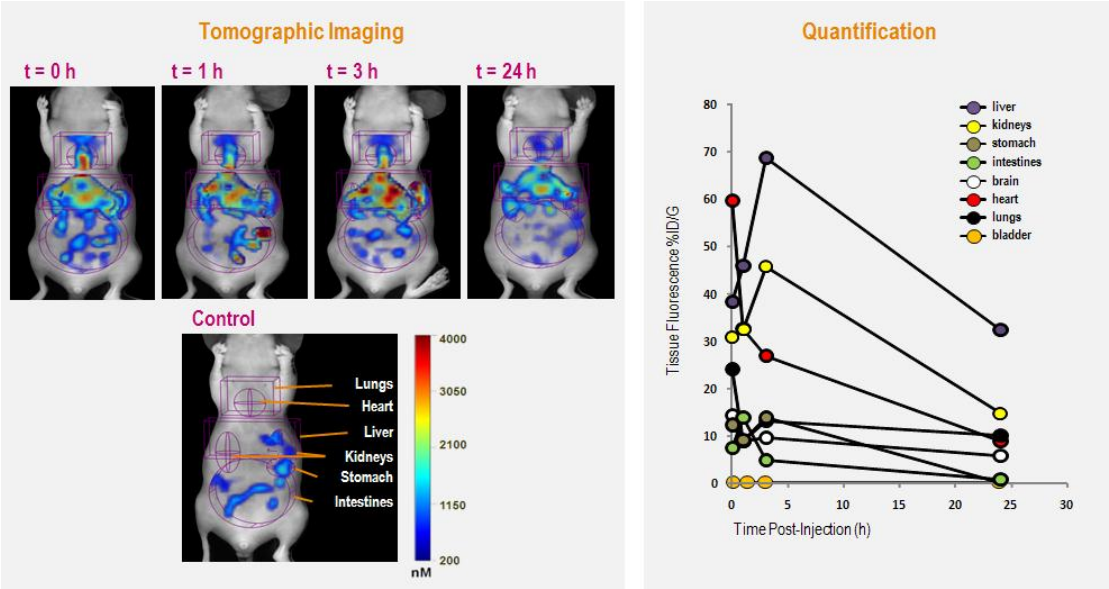
事实上，直接通过荧光染料标记药物注入体内的方式存在诸多问题，如低靶向性、低药效性、免疫排斥、药物毒性问题等。因此，构建新型药物载体也是目前药物研究的热点之一，应用小动物活体光学成像技术同样可以在这一领域发挥作用。如下图所示为研究人员通过小动物活体光学成像技术观测一种新型纳米共聚物给药载体在体内运载吗啉基反义寡核苷酸靶向治疗肿瘤的实验。此类给药载体包含多种组分，如起整体保护作用的外层多聚苹果酸骨架及聚乙二醇、起肿瘤靶向作用的抗体连接组分、药物释放组分、荧光染料结合位点等。结果表明，通过应用新型纳米给药载体可以有效提升药物的靶向治疗效果。



上图左：新型纳米共聚物给药载体结构示意图；上图右：应用 IVIS 成像系统观测不同时间点药物运载系统在体内的分布及对肿瘤的靶向。

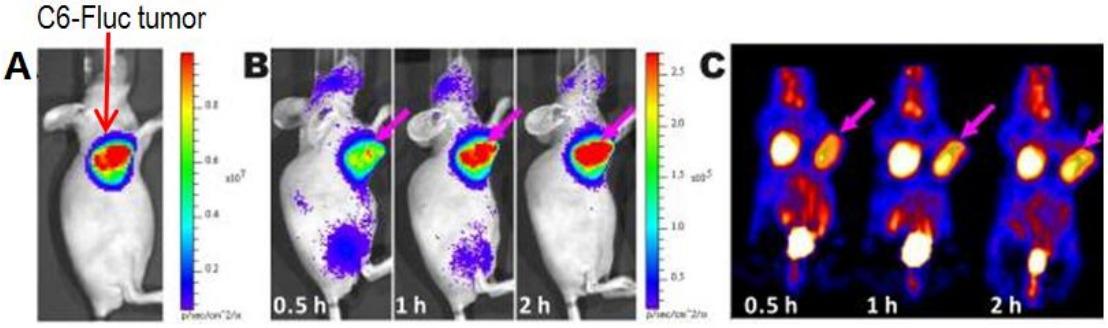
在研究药物靶向的同时，了解不同时间点药物在动物体各个器官的分布及最终代谢情况同样必不可少。Revvity的 FMT 小动物活体荧光断层成像系统可以很好的满足

此类应用需求。应用 FMT 成像系统，能够对荧光标记的药物在深层器官的分布进行断层扫描及三维重建，获得真实准确的三维定量数据，进而对药物的体内分布代谢情况作出正确分析。如下图：



上图左：利用 FMT 成像系统观测不同时间点经荧光染料 VivioTag 680 标记的 BSA 在小鼠不同器官的分布；上图右：不同时间点不同器官 BSA 分布的定量结果。

应用活体荧光成像技术进行药物分布的观测目前主要局限于对生物大分子药物的研究，而对天然或化学小分子药物的分布代谢研究主要依靠的是放射性核素标记成像（PET 或 SPECT），原因是用相对大分子量的荧光染料标记小分子药物，则荧光染料本身即会对小分子药物在体内的分布代谢产生影响，因此无法将活体荧光成像技术应用于此类研究。然而，科研人员最近发现应用高灵敏度的 IVIS 活体光学成像系统可以观测到放射性核素在小鼠体内发出的光学信号，其所依据的是切伦科夫辐射（Cherenkov Radiation）原理，由此拓展了活体光学成像技术的应用范畴，即利用活体光学成像系统观测经放射性核素标记的小分子药物在体内的分布代谢。



切伦科夫辐射成像：应用 IVIS 成像系统结合[^{18}F]FDG 放射性探针观测肿瘤。A.肿瘤生物发光成像结果；B.应用 IVIS 系统进行切伦科夫辐射成像，观测不同时间点[18F]FDG 在肿瘤部位的代谢；C.应用 PET 系统成像，观测不同时间点[^{18}F]FDG 在肿瘤部位的代谢，结果与 B 一致。

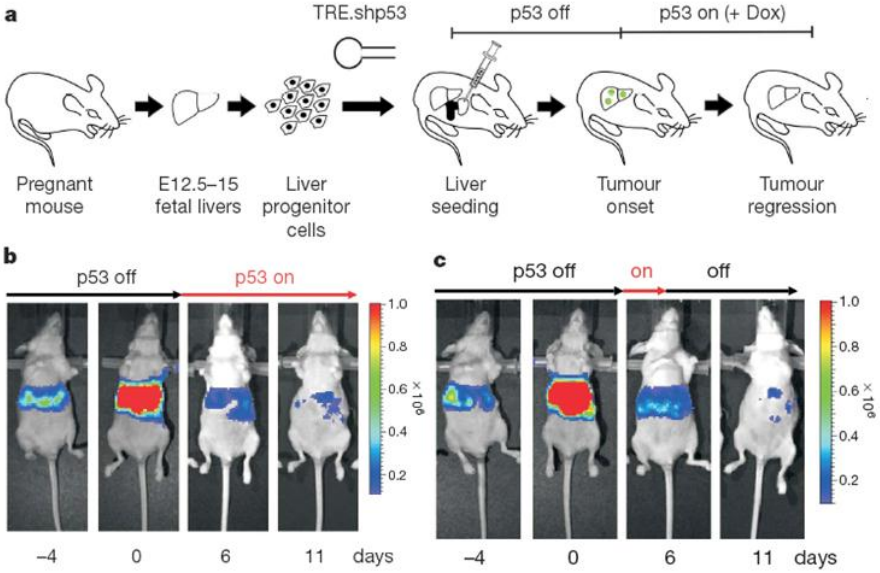
三.癌症分子机理研究

对于癌症分子机理的研究之前一直局限于体外水平，体外研究的缺陷在于无法模拟肿瘤在动物体内真实的生理微环境，因此，单一的体外研究结果并不能完全反映癌症的发生发展机理。小动物活体光学成像技术使科研人员能够进一步将癌症分子机理的研究由体外拓展至体内，如在活体动物水平研究癌症相关基因在癌症发生发展进程中的作用、观测肿瘤发生发展过程中特异性分子事件的发生等。

1、应用生物发光技术研究癌症相关基因的作用

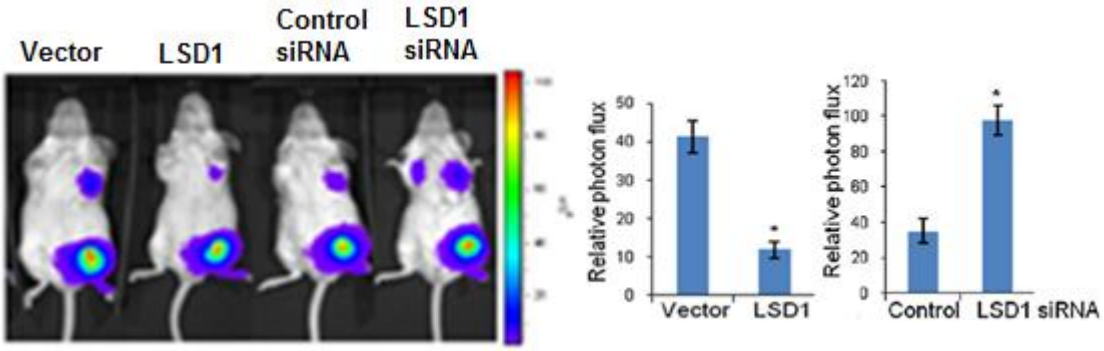
应用生物发光技术进行癌症相关基因的研究方法，主要利用荧光素酶标记特定基因，构建特定基因-荧光素酶的共表达载体，通过荧光素酶产生的生物发光信号反映该基因的表达情况，研究该基因的相关作用。以下几个例子是应用生物发光技术研究癌症相关基因在不同肿瘤模型中作用：

p53 是调节细胞正常生命活动的一种重要基因，控制着细胞周期的启动。p53 也同时被认为是一种重要的抑癌基因，在人类 50%以上的肿瘤组织中均发现了 p53 基因的突变，这是肿瘤中最常见的遗传学改变，说明该基因的改变很可能是人类肿瘤产生的主要发病因素。下图所示是发表于 2007 年 Nature 杂志上的一篇研究 p53 抑癌作用的文献结果。研究者将一个同时带有致癌基因 ras、四环素反式激活因子 tTA (‘tet-off’)及四环素依赖性 p53 shRNA 的逆转录病毒表达载体与荧光素酶基因质粒共转染从小鼠胚胎提取的成肝细胞，并将转染细胞接种于小鼠肝脏，观测 p53 基因表达关闭或开启对于肝癌发生或消亡的作用。结果显示，当 p53 的表达被 shRNA 抑制时，通过生物发光观测到的肿瘤信号逐渐增强，而当给小鼠注入强力霉素（doxycycline）开启 p53 的表达后，肝癌细胞的生物发光信号逐渐减弱，说明 p53 的表达能够抑制肿瘤的生长并促使肿瘤消亡。



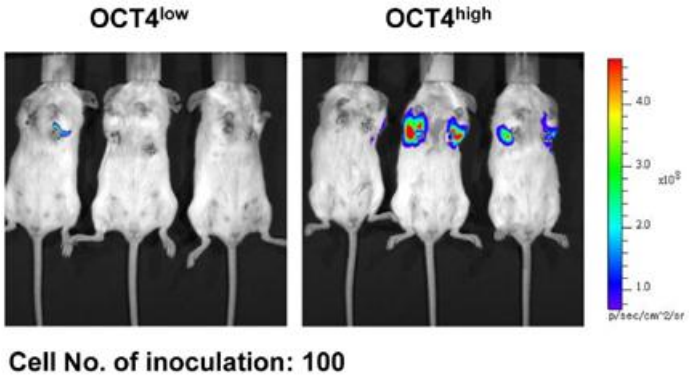
p53 基因的抑癌作用：上图 a，实验设计示意图；上图 b，关闭-开启 p53 的表达对肿瘤发展的影响；上图 c，关闭-开启-再关闭 p53 的表达对肿瘤发展的影响。

乳腺癌是女性最常见的恶性肿瘤之一，而乳腺癌转移是导致患者死亡的主要原因，乳腺癌转移的分子机理目前还不完全清楚。LSD1 是第一个被发现的组蛋白去甲基化酶，理论上对基因转录起广泛调控作用，但近期研究却表明 LSD1 只参与一些特异的细胞信号通路的调控而且与多种肿瘤的发生发展高度相关。北大医学部尚永丰教授课题组应用 IVIS 活体光学成像系统观测到 LSD1 能抑制乳腺癌的侵袭和转移，从而揭示了 LSD1 这一表观调控因子在抑制乳腺癌转移中的重要作用，并为乳腺癌转移的干预提供了新的分子靶点。上述结果发表于 2009 年 Cell 杂志。



LSD1 对乳腺癌转移的抑制作用：将带有 LSD1 或 LSD1 siRNA 或相应对照的表达载体通过慢病毒转染经荧光素酶标记的人乳腺癌细胞株 MDA-MB-231-Luc-D3H2LN，并原位接种于小鼠腹部乳腺脂肪垫，观测 LSD1 的表达与抑制对乳腺癌细胞肺部转移的影响。上图左：应用 IVIS 系统进行生物发光成像结果；上图右：光学定量结果。

肿瘤细胞生长、转移和复发的特点与干细胞的基本特性十分相似，因此，有学者提出肿瘤干细胞（Cancer\Tumor Stem Cell, CSC\TSC）的理论。肿瘤干细胞可以长时间处于休眠状态并具有多种耐药分子而对杀伤肿瘤细胞的外界理化因素不敏感，导致肿瘤往往在常规治疗方法消灭大部分普通肿瘤细胞后一段时间复发。因此，如果能够寻找到肿瘤干细胞特异性治疗靶标，将为肿瘤治疗开辟新的路径。OCT4 是参与调控胚胎干细胞自我更新和维持其全能性的最为重要的转录因子之一，因此，OCT4 可能是杀伤肿瘤干细胞的潜在靶点之一。下述实验是应用 IVIS 系统观测 OCT4 在乳腺癌细胞成瘤中的作用。研究者将带有 OCT4 基因的载体转染经荧光素酶标记的鼠源乳腺癌细胞株 4T1-luc，并分选出高表达及低表达 OCT4 基因的细胞株，分别原位接种于小鼠胸部乳腺脂肪垫，观测结果显示 OCT4 高表达乳腺癌细胞株具有更高的成瘤性。

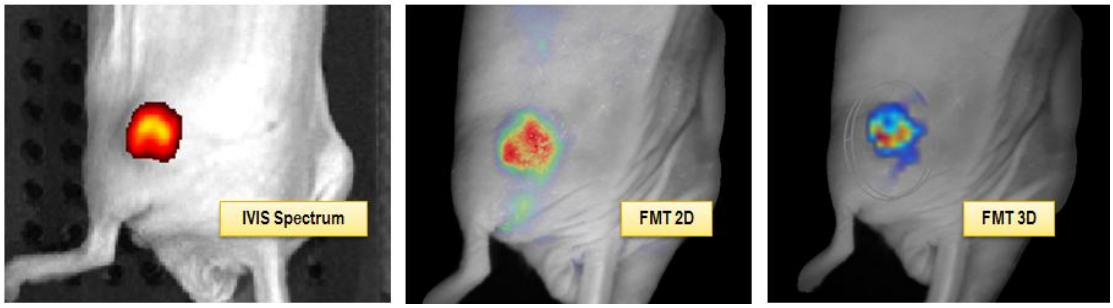


2、应用功能性荧光试剂观测肿瘤内部特异性分子事件的发生

肿瘤发展进程中伴随着诸多分子事件的发生，如某些蛋白酶的表达特异性升高、某些表面标识物的特异性表达、肿瘤周边血管的新生、肿瘤组织局部缺氧等，通过观测这些分子事件能够判断肿瘤的发展程度并作出预后。Revvity提供了一系列应用于肿瘤研究的功能性荧光试剂，使上述观测成为可能。以下为具体应用实例：

应用 PSA 750 FAST 酶激活类荧光试剂观测 PSA^+前列腺肿瘤

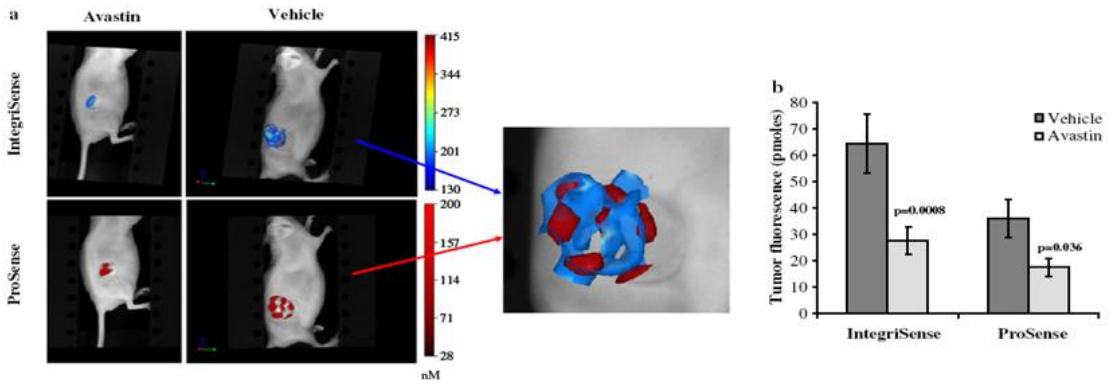
前列腺特异抗原(Prostate Specific Antigen，PSA) 主要是由前列腺上皮细胞产生的蛋白分解酶，正常情况下被分泌入前列腺液或精液中以有活性的游离形式存在，血清中的 PSA 主要以结合形式存在。正常及良性前列腺增生的前列腺上皮均可分泌游离或结合形式的 PSA，但具有酶活性的 PSA 只存在于恶性前列腺肿瘤中。PSA 750 FAST 是一种只能被具有酶活性 PSA 特异性激活的荧光试剂，因此可用于监测前列腺肿瘤的恶性程度。



应用 IVIS Spectrum 及 FMT 成像系统结合 PSA 750 FAST 荧光试剂对裸鼠皮下接种的人前列腺肿瘤 PSA+ LNCaP 进行活体光学成像，成像时间为试剂尾静脉注射后 6h。

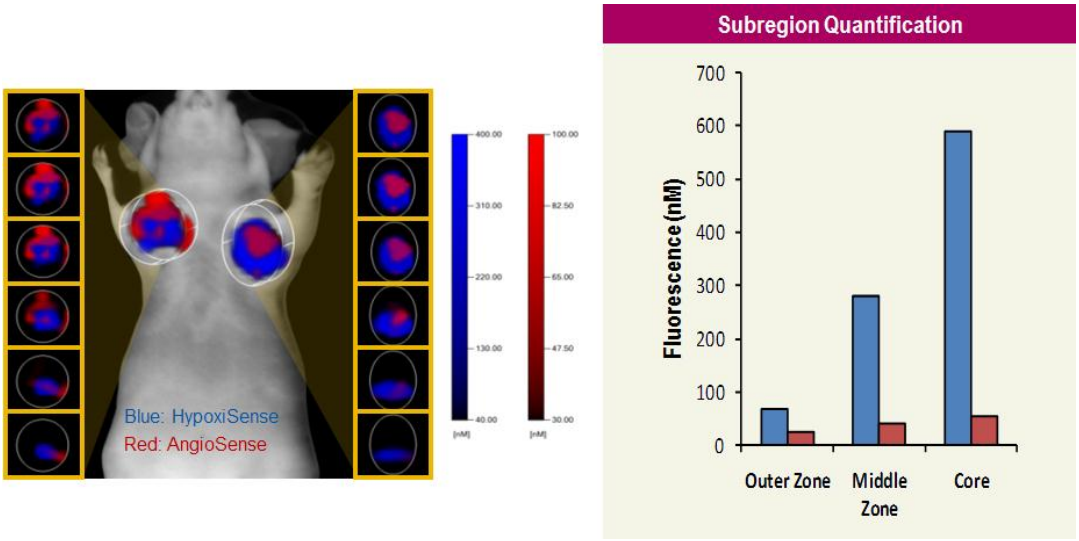
应用 IntegriSense 及 ProSense 荧光试剂观测肿瘤血管新生及组织蛋白酶的表达

肿瘤的发生发展伴随着诸多分子事件的共同发生，应用不同种类的荧光试剂，可以实现在一个实验中观测肿瘤内部的多个生物学进程。如下图所示，在一个实验中同时利用 IntegriSense 及 ProSense 两种荧光试剂对肿瘤进行观测：应用 IntegriSense750 靶向类荧光试剂可以靶向监测肿瘤血管上皮特异性表达的整联蛋白 αvβ3 而反映肿瘤的血管新生；而应用 ProSense680 酶激活类荧光试剂能够监测肿瘤细胞中组织蛋白酶的活性，进而揭示两种对象在肿瘤内部的不同分布及药物（Avastin）治疗后的不同变化。

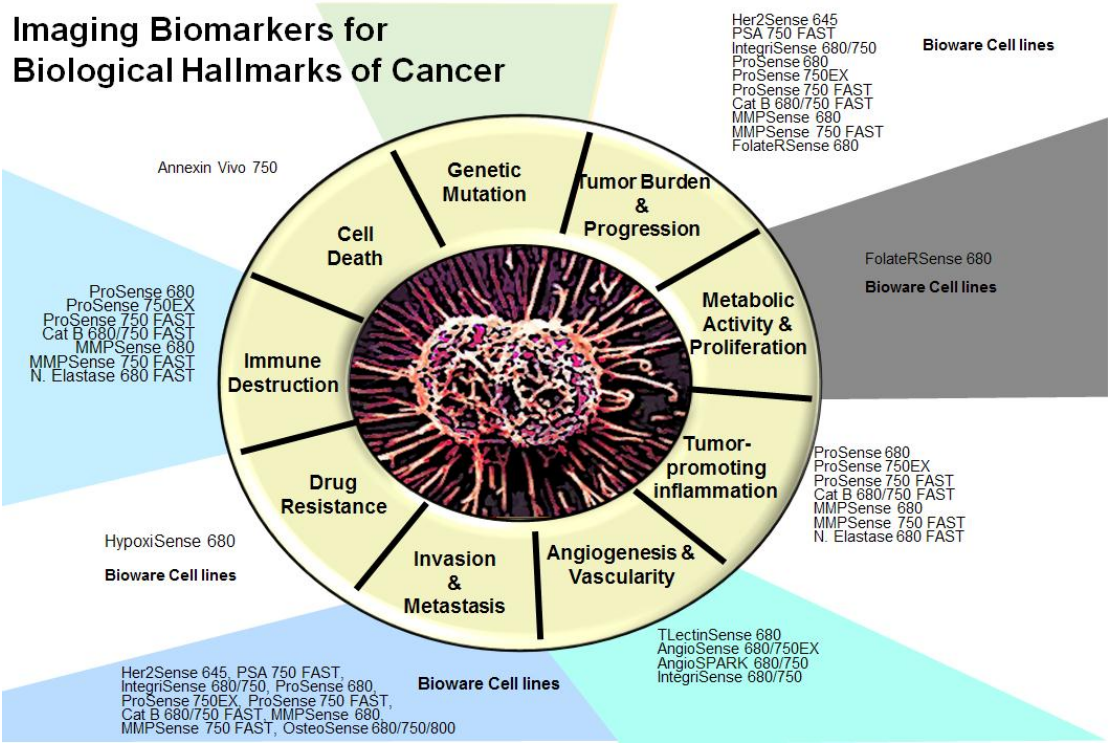


应用 HypoxiSense 及 AngioSense 荧光试剂观测肿瘤微环境

肿瘤的发生和转移与肿瘤细胞所处的内外环境有着密切关系，了解肿瘤微环境对于肿瘤的诊断、防治和预后有着重要意义。下图所示为利用监测肿瘤组织缺氧的 HypoxiSense 靶向类荧光试剂与监测肿瘤血管生成的 AngioSense 血管生理类荧光试剂共同观测小鼠皮下接种的人宫颈癌肿瘤微环境。其中，HypoxiSense 能够特异性靶向缺氧肿瘤细胞表面上调表达的碳酸酐酶 9（CAIX），进而表征肿瘤的缺氧区域；而 AngioSense 通过富集于由于肿瘤血管新生而引发的血管渗漏区域，进而表征肿瘤的血管富集区域。定量结果显示缺氧部位主要位于肿瘤内部中心区。



应用 FMT 成像系统结合 HypoxiSense680 及 AngioSense750 荧光试剂观测裸鼠胸部脂肪垫接种的人宫颈癌肿瘤微环境，并进行定量分析。



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