小动物活体光学成像技术在感染性疾病研究中的应用

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，感染性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感染性疾病研究中，常用的标记方法及应用领域包括：1、利用萤火虫荧光素酶基因、海肾荧光素酶基因或细菌荧光素酶基因标记细菌、病毒、真菌、寄生虫等病原体，在活体水平观测这些病原体在动物体内的感染情况及抗生素、疫苗等药物的治疗效果；2、通过荧光素酶基因或荧光蛋白基因标记免疫细胞，以及利用特定基因-荧光素酶基因转基因动物，观测病原体感染所引发的机体免疫应答及致病机理。下面结合一些具体实例进行阐述：

一.长时间观测病原体在动物体内的动态感染情况

利用 PCR、免疫切片等传统方法对感染性疾病进行研究时，需要耗费大量的人力物力，且不能实现在同一只活体小鼠中长期观测病原体的动态感染情况，因而无法获得准确的重复性数据。小动物活体光学成像技术的出现，使得研究者能够通过一定的方式对细菌、病毒、真菌、寄生虫等病原体进行光学标记，并利用活体光学成像系统长期观测病原体在体内的动态感染情况，在节省实验耗材及简化实验操作的同时，可获得更加直观准确的实验结果。

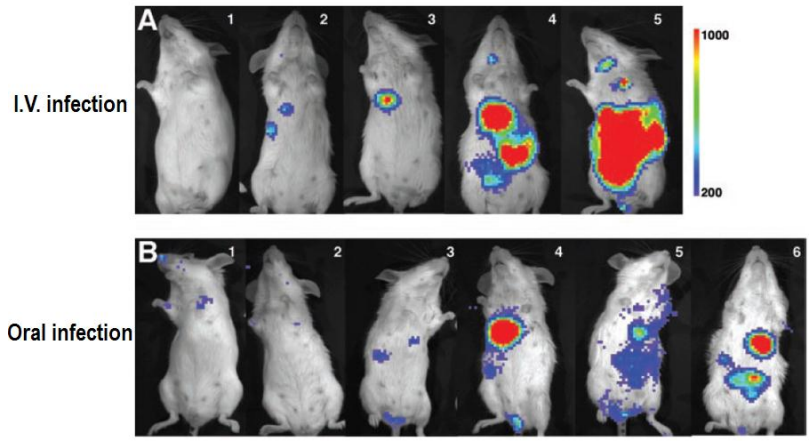
在观测细菌感染方面，研究者既可利用萤火虫荧光素酶基因、海肾荧光素酶基因等常用于标记真核细胞的报告基因进行标记，也可利用从某些发光细菌中提取的 lux 发光基因操纵子进行标记。后者的好处是，lux 操纵子中已含有表达荧光素酶及其底物的序列，因此无需再外源注射底物即可成像。Revvity提供多种商业化的经细菌荧光素酶基因标记的生物发光细菌菌种（如下图所示）：

菌种名称	菌种来源	货号
大肠杆菌	EPEC WS2572 ETEC WS2583	119223 119225
流感嗜血杆菌	ATCC 51907	119224
肺炎克雷伯菌	93A 5370	119227
李斯特菌	ATCC 23074 10403S (Serotype 1/2a wild-type strain)	119237 119238
绿脓杆菌	ATCC 19660 PAO1	119228 119229
奇异变形杆菌	ATCC 51286	119236
金黄色葡萄球菌	8325-4 ATCC 12600 I6-MRSA ATCC 33591 ATCC 49525 UAMS-1	119239 119240 119241 119242 119243 119244
痢疾杆菌	88A6205. Clinical isolate	119231

菌种名称	菌种来源	货号
肺炎链球菌	D39 Serotype 2 HUS-TMBIG, Serotype 19A A66.1, Serotype 3 EF3030, Serotype 19F 140301, Serotype 14	119245 119246 119247 119248 119249
肺炎链球菌	230401 Serotype 23	119321
肺炎链球菌	TIGR Strain Serotype 4	119322
产脓链球菌	Strain 591, Group A, Serotype M49	119250
鼠伤寒沙门菌	SL1344 FDA1189	119230 119235
小肠结肠炎耶尔森菌	91A1854 Clinical isolate WS2589	119232 119233
假结合性棒菌	YPIIIpYV (Type III secretion system), clinical isolate	119234

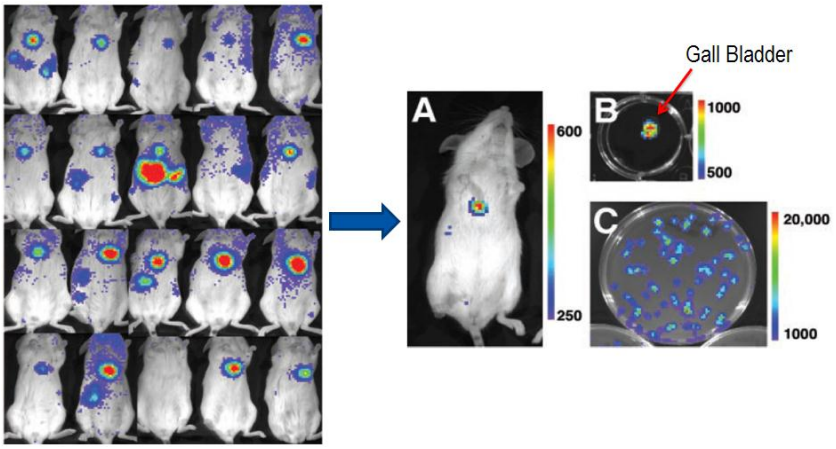
研究者通过购买这些生物发光细菌，即可立即开展相关研究，无需自行标记。如 Hardy 等利用 IVIS 系统观测了细菌荧光素酶基因标记的单核细胞增多性李斯特菌

（*Listeria monocytogenes*）在小鼠体内的时空分布，如下图：



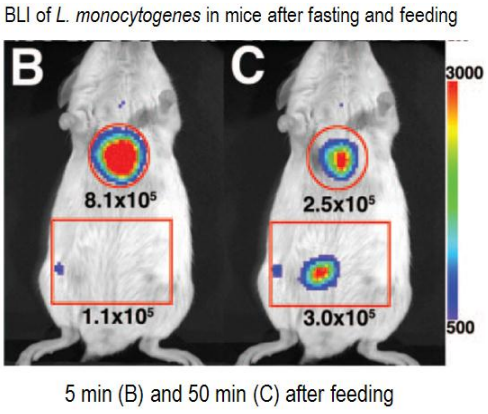
上图：应用 IVIS 系统观测不同时间点李斯特菌在小鼠体内的感染情况。A.尾静脉注射；B.口腔注射。

研究者在通过尾静脉注射李斯特菌感染多只小鼠后发现，几乎在所有被感染小鼠中，该细菌都会特异性分布于小鼠胸部，经手术将发光组织取出后发现，细菌主要集中于胆囊内腔（the lumen of the gall bladder），如下图所示。细菌在胆囊内腔的存留是一个非常危险的信号，因为胆囊内腔由于含有高浓度的胆汁而导致免疫细胞无法进入发挥免疫保护作用，并且胆囊本身又对抗生素具有抵抗性，因此，细菌可以在此区域长期潜伏并随时发作。



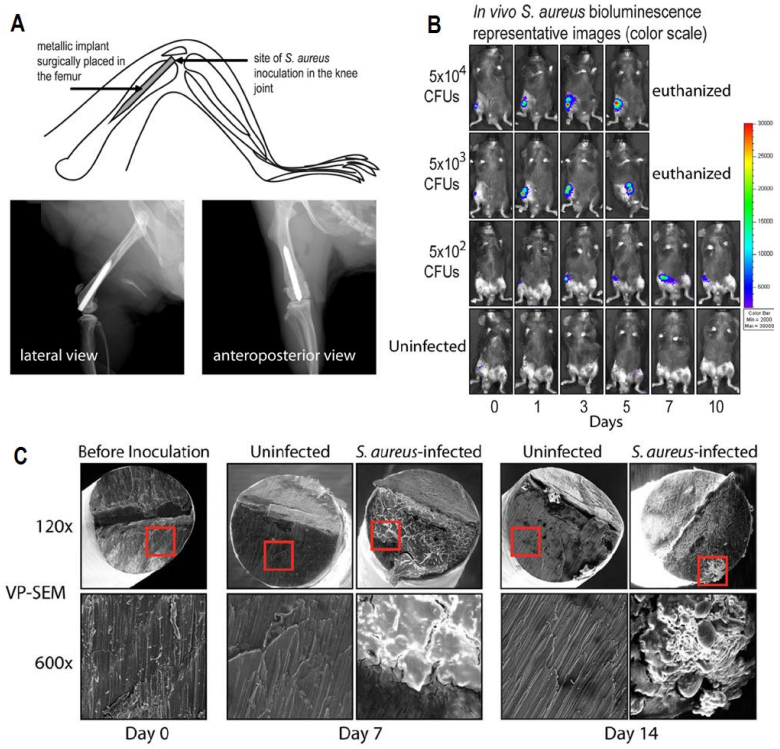
上图：应用 IVIS 系统观测到李斯特菌在胆囊内腔的特异性分布。左：感染 25 只小鼠，在 24 只中观测到李斯特菌在胆囊内腔的分布；右：将胸部发光组织取出后确认为胆囊内腔。

研究者接下来探讨了李斯特菌在胆囊内腔的分布是否具有传染性。由于胆囊在机体未进食时会大量存储由肝脏分泌的胆汁而处于扩张状态，而当机体进食后，胆囊会收缩并将胆汁通过胆管排入小肠而辅助对食物中的脂肪进行消化。因此，研究者通过对被感染的小鼠禁食后再喂食，观测李斯特菌是否能够通过胆汁排泄途径而进入消化道。结果显示，李斯特菌确实能够通过胆汁排泄途径而进入小肠（如下图），并可能通过消化道的排泄进入外界环境而具有传染性。综上所述，研究者利用活体光学成像技术，系统的研究了李斯特菌在小鼠体内的感染分布、潜伏及潜在的传染途径，为该类疾病的治疗提供了依据。



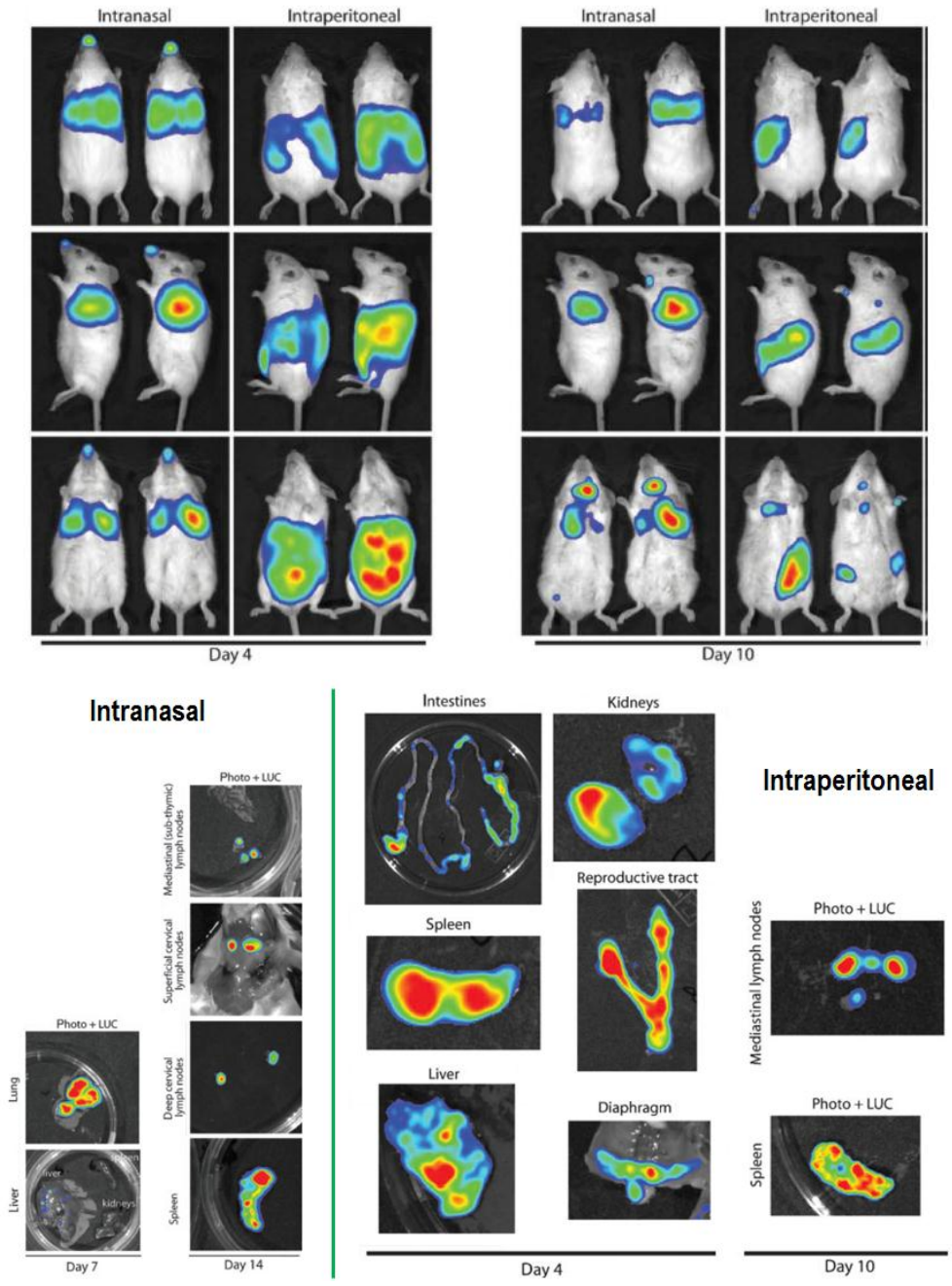
上图：应用 IVIS 系统观测李斯特菌经胆汁排泄途径由胆囊进入消化道。B、C 分别为再喂食后 5min 及 50min 成像结果。

对细菌生物膜（Bacterial Biofilm）的研究也是细菌感染研究的一大热点。细菌生物膜是细菌在生长过程中附着于物体表面而形成的由细菌细胞及其分泌的含水聚合性基质（主要为胞外多糖）等所组成的膜样多细菌复合体。生物膜是细菌适应生存环境而形成的与游走态细胞相对应的存在形式，它具有很强的抵抗机体免疫和抗生素的能力，在临床上形成难治性感染。Bernthal 等通过在小鼠下肢股骨远端插入接种了生物发光金黄色葡萄球菌（*S. aureus*）的不锈钢针，模拟了人关节成形手术后经常发生的细菌生物膜形成，并用 IVIS 系统及变压扫描电镜（VP-SEM）观测了细菌感染及生物膜的形成（如下图）。这种实验模型的建立为开发有效的治疗手段及抗菌剂提供了有力工具。



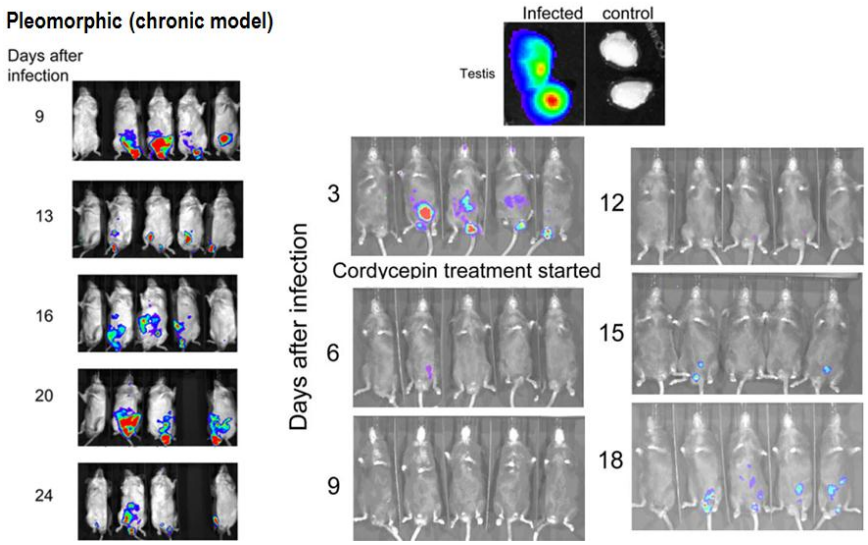
上图：通过模拟实验观测关节成形术后 *S. aureus* 的感染及生物膜的形成。A.模拟实验示意图及钢针移植后 X 光成像结果；B.应用 IVIS 系统观测不同数量生物发光 *S. aureus* 在关节处的感染情况；C.应用 VP-SEM 观测细菌生物膜的形成。

在病毒研究方面，研究者通常将萤火虫荧光素酶基因插入病毒 DNA 中标记病毒，进而观测病毒在活体动物体内的动态变化。Milho 等人利用 IVIS 系统观测比较了经不同途径感染小鼠的鼠源疱疹病毒（murine herpesvirus-4, MuHV-4）在小鼠体内的感染分布情况。结果显示，经鼻腔感染的病毒，在感染早期主要分布于小鼠的鼻腔及肺，随着时间的延长，病毒将集中分布于颈部淋巴结及脾等淋巴组织；经腹腔接种的病毒，在感染早期分布于腹部的多个器官（如肝、脾、肾、肠、生殖系、隔膜），所时间的延长，病毒将集中分布于脾及肠系膜淋巴结。因此，病毒的不同感染途径可能会引起不同的发病机制。



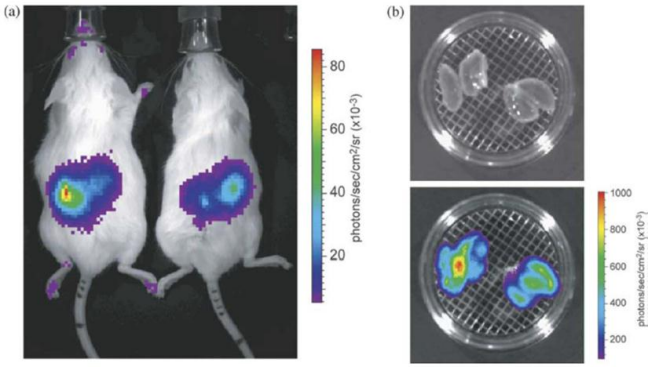
上图：应用 IVIS 系统观测 MuHV-4 病毒经不同途径接种后的感染情况。上，活体成像结果；下，将不同器官取出后体外成像结果。

与细菌、病毒感染研究类似，研究者也可通过荧光素酶基因标记寄生虫，观测其在活体动物体内的感染情况。如 Claes 等人利用 IVIS 系统观测了经海肾荧光素酶基因标记的布氏锥虫（*Trypanosoma brucei*）在小鼠体内的感染情况。体内及体外成像结果显示，经腹注射后，布氏锥虫选择性分布于睾丸。布氏锥虫在睾丸的选择性分布可能会使其避开药物的作用，因为许多药物无法通过睾丸-血管屏障而进入睾丸。随后的给药实验印证了这种推断，在布氏锥虫感染小鼠 5 天后，用虫草素（cordycepin）连续进行三天处理，停药后在第 15 天发现睾丸处重新出现布氏锥虫生物发光信号。这一研究为开发治疗布氏锥虫感染的有效药物提供了依据。



上图：应用 IVIS 系统观测布氏锥虫在小鼠体内的感染情况。左，感染后不同时间点活体成像结果；右上，取出睾丸后体外成像结果；右下，虫草素对布氏锥虫的治疗效果观测。

近些年，研究者也开始利用荧光素酶基因标记真菌，并通过活体光学成像系统观测真菌在动物体内的感染情况。Doyle 等人应用萤火虫荧光素酶基因标记了从临床病例中获得的白色念珠菌（*Candida albicans*），将该真菌尾静脉注射入小鼠体内构建慢性败血症感染模型，利用 IVIS 系统观测了生物发光白色念珠菌在小鼠体内的感染情况。体内及体外成像结果显示，随感染时间的延长，该菌主要分布于小鼠肾脏（如下图）。

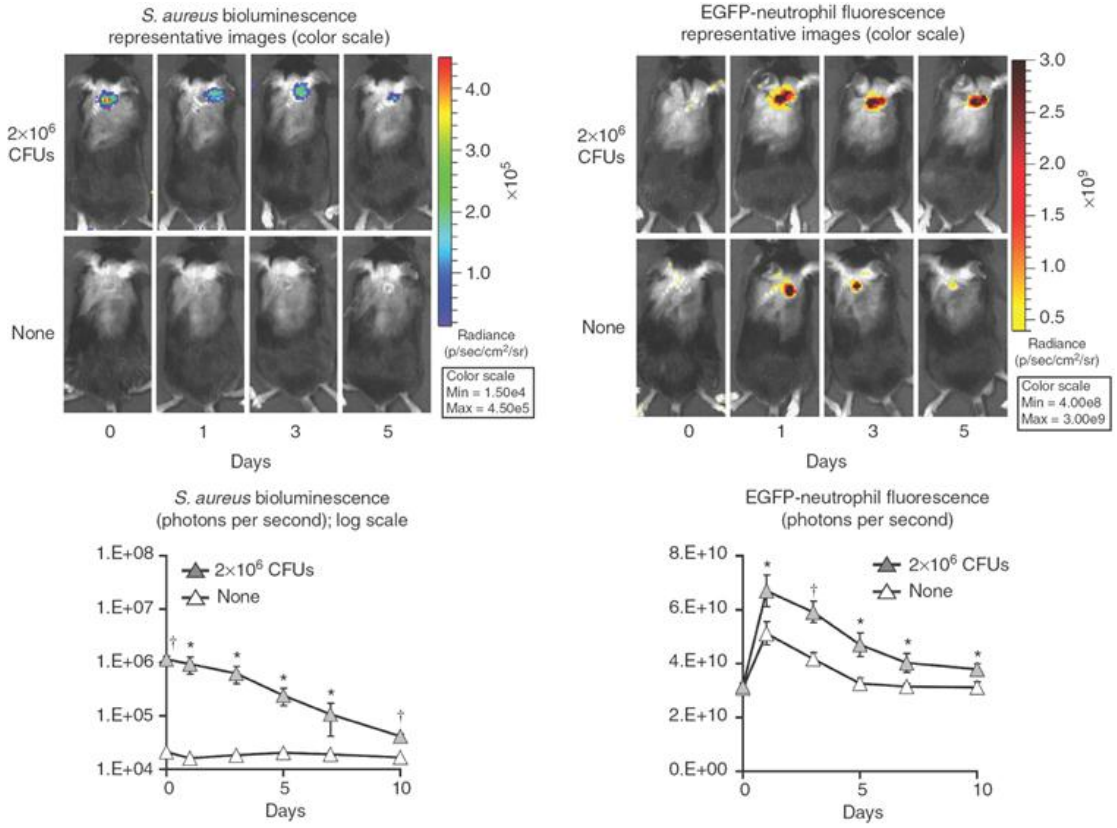


上图：应用 IVIS 系统观测白色念珠菌经尾静脉注射后在小鼠体内的感染情况。A.体内成像结果；B.体外成像结果。

二.监测抗感染免疫反应

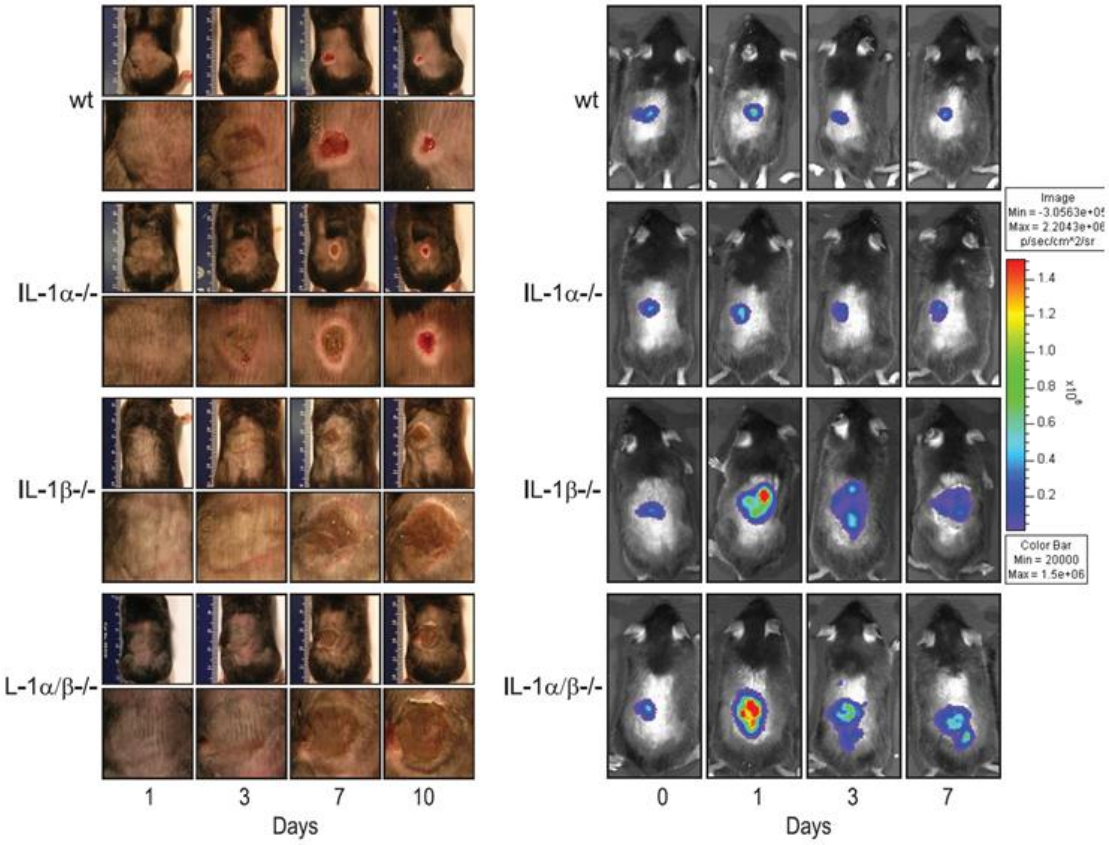
在利用小动物活体光学成像技术观测病原体在动物体内感染情况的同时，还可应用该技术观测机体对病原体入侵的免疫反应。此类应用可以通过三种方式实现：1、利用报告基因标记在免疫细胞中特异性表达的基因启动子而构建转基因动物，以该转基因动物为实验模型，用经光学标记的病原体对其进行感染，观测病原体感染而引发的免疫细胞应答；2、利用报告基因标记目的基因的启动子构建转基因动物，观测病原体感染后该基因的表达情况，了解免疫应答的分子机理；3、利用某种免疫相关基因被敲除的基因敲除鼠作为实验模型，观测病原体的感染情况，以了解这些基因在免疫反应中的作用。

Cho 等利用 LysEGFP 转基因小鼠作为实验用鼠，应用 IVIS 系统观测了生物发光金黄色葡萄球菌经皮肤伤口感染小鼠后引发的嗜中性粒细胞的免疫应答。由于实验小鼠是 LysEGFP 转基因小鼠，因此其体内的嗜中性粒细胞即为 EGFP 所标记，因此在用生物发光成像模式观测细菌感染的同时，也能通过荧光成像模式观测嗜中性粒细胞在感染部位的聚集。如下图所示，与未经感染的对照组相比，金黄色葡萄球菌的感染引发了大量嗜中性粒细胞在感染部位的聚集，这伴随着细菌感染程度相应地降低，而对照组中少量嗜中性粒细胞的聚集是由于皮肤创伤而引起的免疫反应。



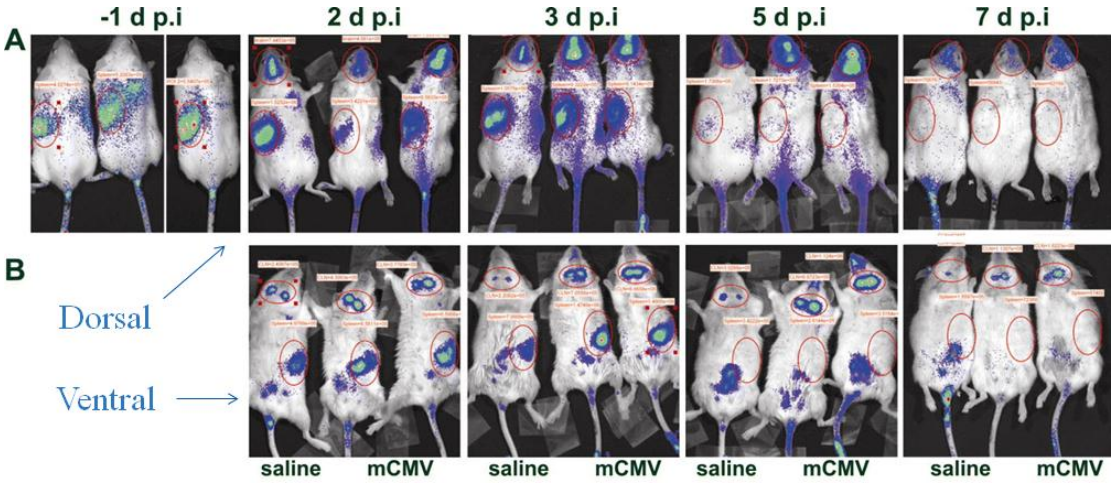
上图：应用 IVIS 系统观测生物发光金黄色葡萄球菌对 LysEGFP 转基因小鼠皮肤伤口的感染及所引起的嗜中性粒细胞的免疫应答情况。左，不同时间点金黄色葡萄球菌感染生物发光成像及定量结果；右，EGFP 标记的嗜中性粒细胞对细菌感染的应答荧光成像及定量结果。

IL-1R 信号通路的激活在嗜中性粒细胞对金黄色葡萄球菌皮肤感染的免疫应答中起重要调控作用，而 IL-1α 和 IL-1β 是激活 IL-1R 信号通路的两种主要配体。Miller 等人通过应用敲除上述两种基因的基因缺陷型小鼠 IL-1α$^{-/-}$、IL-1β$^{-/-}$及 IL-1α/ IL-1β$^{-/-}$，揭示了 IL-1β 在趋化嗜中性粒细胞到达皮肤感染区域所起的重要调控作用。结果显示，金黄色葡萄球菌对野生型小鼠及 IL-1α$^{-/-}$缺陷型小鼠中的感染程度相当，而对 IL-1β$^{-/-}$及 IL-1α/ IL-1β$^{-/-}$缺陷型小鼠的感染程度明显高于前两者，说明 IL-1β 在趋化嗜中性粒细胞对金黄色葡萄球菌皮肤感染的免疫应答中是必须的。



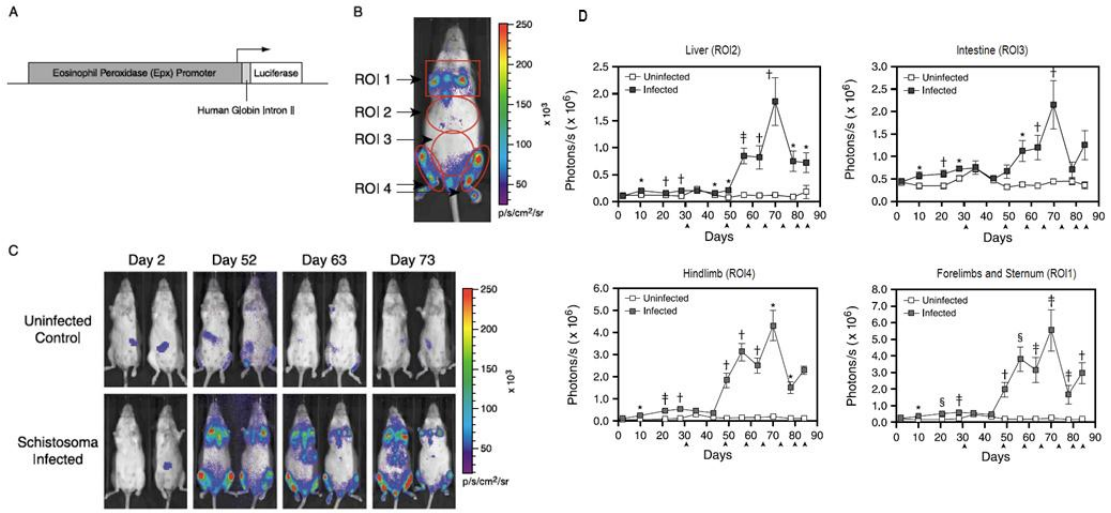
上图：应用 IVIS 系统观测生物发光金黄色葡萄球菌对野生型小鼠及三种基因缺陷型小鼠 IL-1α$^{-/-}$、IL-1β$^{-/-}$和 IL-1α/ IL-1β$^{-/-}$的皮肤感染情况。左，普通相机拍摄图片；右，活体光学成像结果。

Cheeran 等利用从转基因小鼠 Tg(β-actin-luc)中提取的脾细胞及淋巴结细胞，研究了免疫细胞对病毒感染的响应。研究者将提取的发光脾细胞及淋巴结细胞通过尾静脉注入脑室内感染巨细胞病毒的小鼠，利用 IVIS 系统观测了上述免疫细胞在活体动物体内对感染病灶点的浸润。结果显示，在未经病毒感染的正常小鼠体内，移植的淋巴细胞主要聚集于脾内（如下图-1dpi 所示），而当小鼠脑部感染病毒后，这些淋巴细胞会迁移至感染区域而发挥免疫清除作用。



上图：利用 IVIS 系统观测免疫细胞对病毒感染的免疫应答。A、小鼠背部朝上拍摄；B、小鼠腹部朝上拍摄。-1dpi 为病毒感染前 24h 尾静脉注射淋巴细胞成像结果，每张图中从左至右第一只小鼠为注射生理盐水的对照小鼠，第二、三只小鼠为脑室内感染巨细胞病毒的疾病小鼠。

Davies 等利用嗜酸性粒细胞特异性启动子 EPX 控制萤火虫荧光素酶基因的表达，而构建了转基因小鼠 EPX-luc，并用该转基因小鼠作为实验小鼠，观测了由血吸虫（Schistosome）感染而引发的嗜酸性粒细胞的免疫应答。结果显示，在感染后 8 至 10 周，嗜酸性粒细胞主要在肝脏、小肠、上下肢及胸骨中增多，而这种增多是由血吸虫卵在这些区域的沉积所引发，而血吸虫自身也会在早期潜伏性感染时引起小肠中嗜酸性粒细胞的增多。

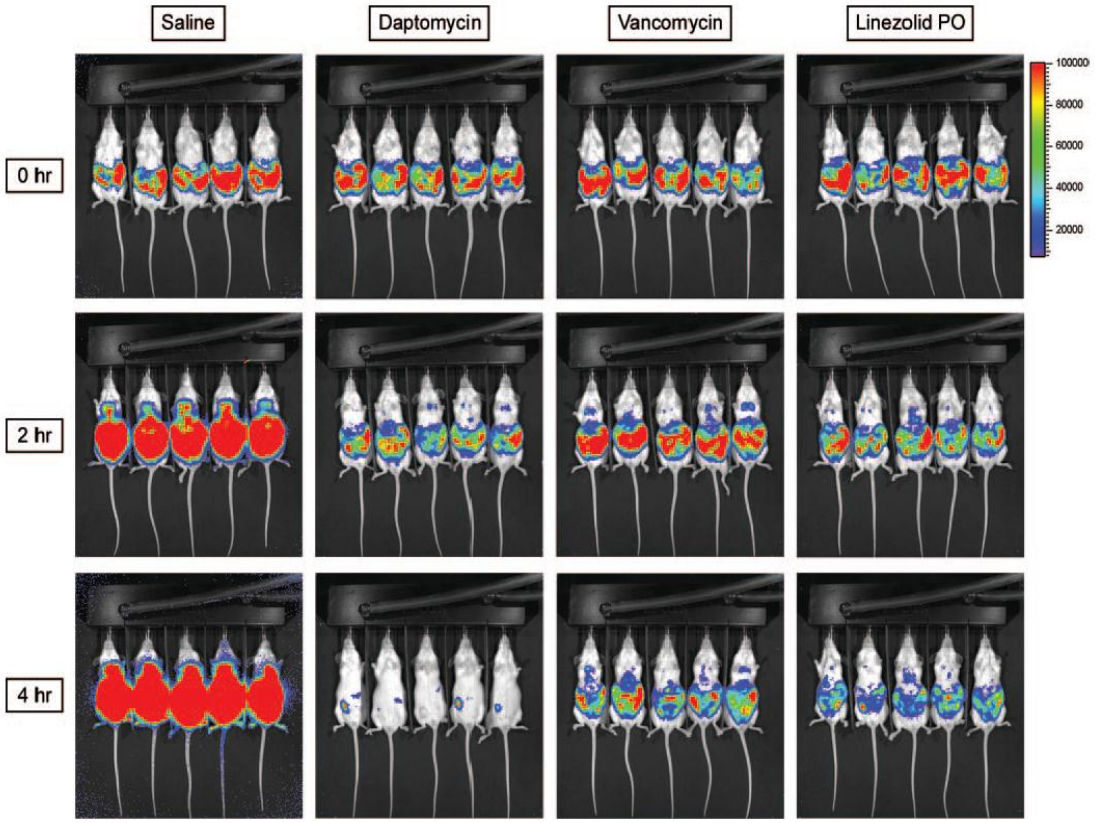


上图：利用 IVIS 系统观测嗜酸性粒细胞对血吸虫感染的免疫应答。A、EPX-luc 表达载体构建示意图；B、感染 70 天后活体成像结果及 ROI 圈选示意图；C、不同时间点由于血吸虫感染而引发的嗜酸性粒细胞在不同部位增多的活体成像结果；D、感染后不同时间点不同部位（肝、小肠、上肢及胸骨、下肢）嗜酸性粒细胞活体成像定量结果。

三.抗生素及疫苗等抗感染药物研发

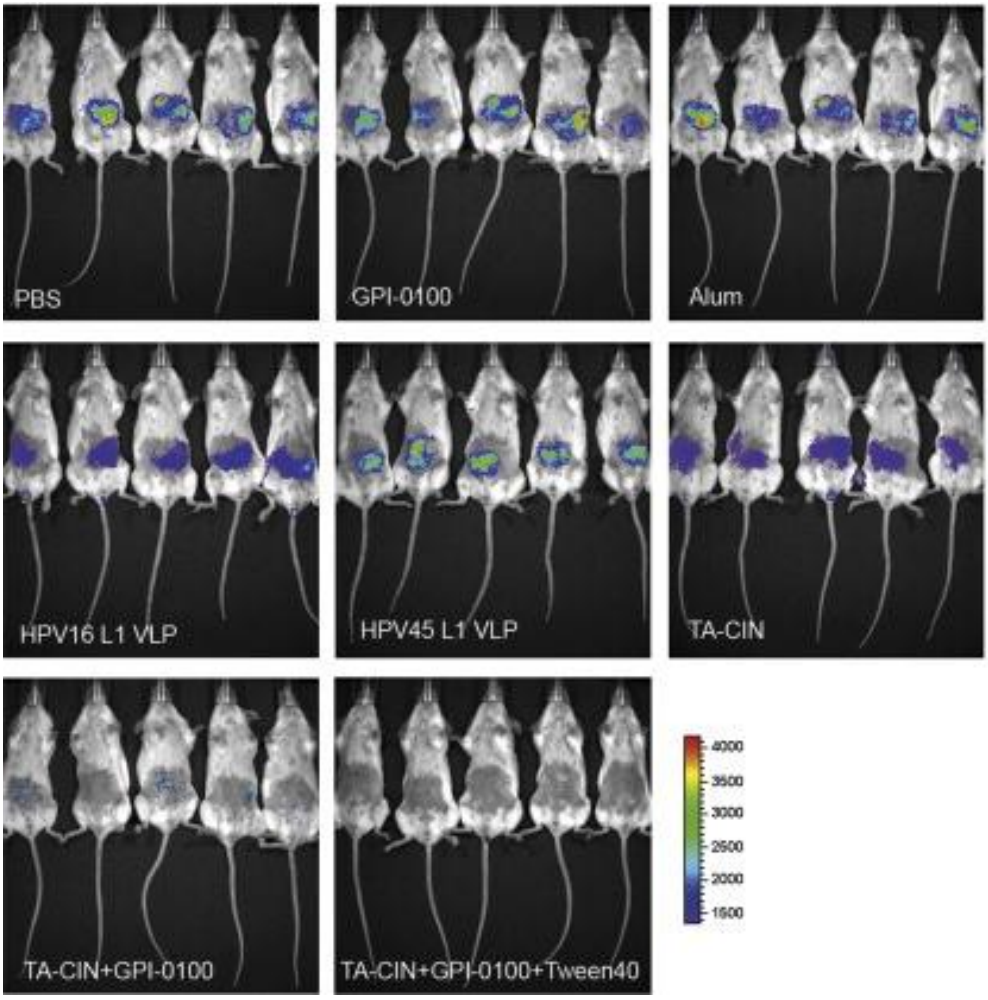
应用传统方式对抗生素、疫苗等抗感染药物在活体水平的研发筛选，需要在给药后处死小鼠，取出感染部位，再通过 PCR、菌落计数、切片观察等方法对药物治疗效果进行评价。这些方式需要耗费大量实验动物、进行繁琐的实验操作，很难实现高通量筛选，且不能利用同一只动物从头到尾的获取实验数据，因此很难获取准确的重复性数据。小动物活体光学成像技术是一种非侵入式活体观测技术，无需在实验过程中处死老鼠，并且可以使用同一批老鼠完成不同时间点的观测，因此已广泛应用于抗感染药物的研发。

抗生素（antibiotics）是由微生物（包括细菌、真菌、放线菌属）或高等动植物在生活过程中所产生的具有抗病原体或其它活性的一类次级代谢产物，可用于治疗各种细菌感染或抑制致病微生物的感染。应用小动物活体光学成像技术可以评价抗生素对病原体感染的治疗效果。达托霉素（Daptomycin/Cubicin）是 Cubist Pharmaceuticals 制药公司研发的已获得 FDA 认证的一种抗生素类药物，可用于革兰氏阳性菌感染而导致的腹膜炎的治疗。该公司在此药物的研发过程中即应用到了小动物活体光学成像技术以评价该抗生素对腹膜炎的治疗效果。研究者应用生物发光金黄色葡萄球菌（S. aureus）通过腹腔注射感染小鼠诱发腹膜炎，之后比较了 Daptomycin、Vancomycin 及 Linezolid 三种抗生素对细菌感染的抑制效果。结果显示，Daptomycin 的治疗效果最好，如下图：



上图：利用 IVIS 系统观测 Daptomycin（50 mg/kg）、Vancomycin（100 mg/kg）及 Linezolid（100 mg/kg）三种抗生素对金黄色葡萄球菌感染的抑制效果。

疫苗是将病原微生物（如细菌、立克次氏体、病毒等）及其代谢产物，经过人工减毒、灭活或利用基因工程等方法制成的用于预防传染病的自动免疫制剂。疫苗保留了病原菌刺激动物体免疫系统的特性。当动物体接触到这种不具伤害力的病原菌后，免疫系统便会产生一定的保护物质，如免疫激素、活性生理物质、特殊抗体等；当动物再次接触到这种病原菌时，动物体的免疫系统便会依循其原有的记忆，制造更多的保护物质来阻止病原菌的伤害。应用小动物活体光学成像技术可以评价疫苗对病原体感染的治疗效果。Karanam 等应用 IVIS 系统观测了联合使用 TA-CIN 疫苗及 GPI-0100 辅药对小鼠预防性接种后，对荧光素酶基因标记的人乳头瘤假病毒 HPV16 皮肤感染的预防治疗效果。结果显示，与单独接种相比，TA-CIN 疫苗及 GPI-0100 辅药的联合使用能够更好的抑制人乳头瘤假病毒的感染，其中 GPI-0100 辅药在诱导体液及细胞免疫应答方面发挥重要作用。



上图：利用 IVIS 系统观测联合使用 TA-CIN 疫苗及 GPI-0100 辅药对 HPV16 感染的预防抑制效果。

IVIS APPLICATIONS IN INFECTIOUS DISEASE RESEARCH

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