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FACT SHEET

神经病理性疼痛之干细胞模型的严谨方法：研究人员指南

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前言 (Introduction)

本情况说明旨在通过总结利用人类干细胞来源的体外模型模拟神经病理性疼痛的核心资源与建议，来建立疼痛研究与干细胞研究之间的桥梁。传统神经病理性疼痛临床前模型在临床转化上的局限性，驱使科学界对于开发稳健的人体实验模型的需求日益增加。为了回应此需求，诱导多能干细胞（iPSC）来源的感觉神经元（induced pluripotent stem cell-derived sensory neurons, iSNs）已脱颖而出，成为具备高度转化潜力的核心实验平台。相较于许多现有方法，这些模型提供了关键优势，包括可扩展性以及模拟人类遗传变异的能力，进而能够直接在人类感觉神经元中进行功能特性分析与药物筛选。

目前已有越来越多的文献利用此技术来模拟各种神经病理性疼痛疾病。这一研究规模的迅速扩张凸显了建立标准化方法学框架的必要性，以确保实验发现的严谨性、可重复性以及临床转化性。重要

的是，基于 iPSC 的神经系统疾病模拟已是一个成熟的领域。该领域中的庞大文献体系[13,15,26]，为感觉与疼痛神经生物学提供了坚实的基础，使得相关最佳实践能够被借鉴并加以应用。

使用 iPSC 模拟神经病理性疼痛疾病的范例 (Examples of neuropathic pain conditions that have been modeled using iPSC)

遗传性疼痛疾病的体外模型已成功在 iSNs 中重现患者特异性的表型（patient-specific phenotypes）。针对因 Nav1.7 功能增强突变所致的遗传性红斑肢痛症模型研究显示，与对照组相比，患者源性 iSNs 的自发性活动、放电与突发放电频率皆有所增加，且具备更高的热敏感性[1,6,37]。在小神经纤维病变（small fiber neuropathy）的患者特异性模型中也观察到了类似的结果。在此研究中，一种使 iSNs 放电行为恢复正常的药物干预，随后成功转译应用于患者身上[41]。相反地，据报道，导致先天性无痛症的 Nav1.7 功能丧失突变，则会如预期般地导致 iSNs 的兴奋性降低[36]。

除了电生理学结果和神经突触生长受损之外，在遗传性感觉神经病变的 iSN 模型中，也有神经营养因子（neurotrophin）信号传导和神经节旁完整性（paranodal integrity）受损的报告[9]。同样地，在法布里病（Fabry disease）的 iSN 模型中，也发现了轴突导向（axon guidance）失调的现象[17]。针对化学治疗引起的周围神经病变之神经毒性研究显示，除了会降低细胞存活率外，还会出现剂量依赖性的形态学改变，例如神经突触生长减少、轴突退缩与碎片化，并伴随神经元损伤、细胞压力和细胞凋亡基因的表达增加[5,20,38,50]。

除了用于模拟神经病理性疼痛疾病外，iSNs 还被用作将动物模型的研究发现转译至人类体外系统的工具，例如：通过炭疽毒素（anthrax toxins）调节 PKA 信号传导，或是通过化学遗传学技术静息（chemogenetic silencing）过度活跃的伤害感受器（nociceptors）[45,60]。

患者招募与干细胞库 (Patient recruitment and stem cell repositories)

在为基于 iPSC 的研究项目招募供体时，必须与主管机关清楚表明伦理审批（ethical approval）的需求，并提供全面的信息以获得患者知情同意（informed consent）。Orzechowski 等人[44]对知情同意材料中应提供的信息进行了建议与总结，其中应包括：研究背景信息、细胞在未来（商业性）研究中的潜在用途、患者材料与细胞系（cell lines）的储存方式，以及如何处理偶然发现的医学诊断。在可行的情况下，应当收集详细的人口学、临床、医学、诊断和遗传数据，并将其与生成的细胞系相结合 [13]。为iPSC 研究所选的患者组群（cohort），应当针对研究的具体科学问题量身定制，并力求获得具有适当代表性和多样性的样本。

除了为新研究重新编程iPSC 细胞系外，还可以从各种细胞银行、储存库或直接从生成并发表该细胞系的实验室，获取来自对照组或疾病背景的、已经过重新编程且通过质量控制的 iPSC 细胞系。以下是全球多能干细胞（PSC）库的列表：African iPSC Initiative、CellBank Australia、Coriell、European Bank for Induced Pluripotent Stem Cells、HipSci、Indian Stem Cell Repository、National Stem Cell Bank Korea、New York Stem Cell Foundation Repository、NINDS Human Cell and Data Repository、RIKEN BRC Japan、the Human Pluripotent Stem Cell Registry、UK Stem Cell Bank 以及 WiCell。

重新编程与 PSC 质量控制 (Reprogramming and PSC quality control)

自从 2006 年发现表观遗传重新编程（epigenetic reprogramming）以来，iPSC 技术已成为一个稳健且被广泛采用的平台，并拥有成熟的实验方案与质量控制标准支持，以确保其高保真度、基因组完整性和生物学相关性。因此，在建立神经病理性疼痛机制模型并生成和使用 iPSC 细胞系时，应当考虑几个关键要素。

用于重新编程的源组织（source tissue）应当经过仔细挑选并明确报告，因为体细胞可能会携带获得性的遗传或表观遗传改变，这些改变在重新编程后仍会持续存[43]。例如，真皮成纤维细胞（dermal fibroblasts）会潜在地积累与紫外线相关或与年龄相关的突变，这些突变可能会在衍生出的 iPSC 细胞系中保留下来[40,56]。在可行的情况下，外周血单核细胞（PBMCs）具有独特的优势，包括易于采集以及较低的环境突变负荷。重新编程应当优先使用基因组非整合型方法（genome-non-integrating approaches）进行，例如仙台病毒（Sendai virus）、游离质粒（episomal plasmids）或基于 mRNA 的方法，以最大程度地减少插入突变（insertional mutagenesis）。iPSC 细胞系应当通过核型分析（karyotyping）或拷贝数变异分析（copy-number analysis）来评估基因组稳定性，且由女性患者供体衍生的细胞系应当评估 X 染色体失活状态，这在遗传性疼痛研究中尤为重要[10]。鉴于多能干细胞对培养条件高度敏感，为了确保实验的可信度，应当定期对 iPSC 培养物进行微生物污染（如支原体 mycoplasma）筛检，并且需要使用化学成分确定的无动物源成分（chemically defined, xeno-free）培养基与基质，以减少批次间差异并提高跨实验室的可复制性。国际干细胞研究学会（ISSCR）近期发布了推荐的标准 [55]，以及关于发表人类多能干细胞研究结果时的建议报告规范 [47]。

分化策略、质量控制与细胞类型验证 (Differentiation strategies, quality control, and cell type validation)

在过去 15 年中，已有多种关于利用多能干细胞进行人类外周感觉神经元体外衍生（in vitro derivation）的实验规范发表[27]。这些实验规范中的大多数可以归纳为以下三种方法之一：

1. 在小分子引导下，将 iPSC 分化为感觉神经元。
2. 在命运决定转录因子（fate-specifying transcription factors）过表达的引导下，将 iPSC 分化为感觉神经元。
3. 从 iPSC 生成稳定的中间态神经前体细胞（neural progenitor）或神经嵴细胞（text crest cell）群体，随后可进一步引导分化为感觉神经元或其他神经嵴衍生物。

大多数已发表的实验规范生成的都是通用的或混合的感觉神经元群体[2,4,14,19,22,31,39]。然而，一些实验方案报道了可生成富含伤害感受性（nociceptive）[3,7,11,46,51]、机械感受性（mechanoreceptive）[21,42,52]或本体感受性（proprioceptive）[12,21]感觉神经元的培养物，或者可以在分化后对混合感觉神经元培养物进行特定亚型的分选[49]。

在执行分化规范时，对生成的细胞类型进行验证与特性分析至关重要。iSNs 的身份应当通过检测通用感觉神经元标志物（如 peripherin、ISLET1、BRN3A）以及亚型特异性标志物（如 TRPV1、TRKA、Nav1.7、Nav1.8）的共同表达来建立验证[28]。此外，电生理学功能可以通过膜片钳（patch clamp）和多电极阵列（multielectrode array, MEA）记录，并结合特异性药理学激动剂或阻断剂来进行评估[23,28]。需要注意的一点是：干细胞来源的体外模型模拟的是人类的发育过程；因此，它们的成熟状态与功能性是一个随着培养进程而不断演变的动态目标。已有研究表明，阿片受体虽然在 iSNs 早期阶段就有表达，但只有在延长培养时间后才会启动功能性细胞内信号传导[48]；此外，Nav1.7 在细胞膜上的稳健定位（membrane localization）同样需要随着培养时间的推移才会显现[32]。因此，当针对一个新靶点进行研究时，建议在选定的 iSN 模型系统中对该靶点的表达、定位及功能进行长期的特性分析。利用现有常用方案生成的 iSNs 已发表的转录组数据，可用于为初始模型的选择提供参考参考[e.g., 33]。

统计学考量与实验设计 (Statistical considerations and experimental design)

与体内研究相同，将基于 iPSC 模型的发现转化至临床需要严谨的实验设计与适当的统计学方法，且必须考虑多个方面。主要结局指标（Primary outcomes）应当预先（a priori）定义，且选定的检测方法应当直接测量研究所涉及的生物学概念[5,58]。重要的是，通常需要多种互补的检测方法来验证研究发现，尤其是在模型开发阶段。鉴于用于生成感觉神经元的分化方案具有多样性，神经元的成熟度必须经过仔细评估与报告。仅凭标志物表达不足以定义功能成熟度；因此，还应当评估离子通道功能与兴奋性，优先使用膜片钳电生理学和/或多电极阵列（MEA）记录，以确保发育状态不会引入非

预期的变异性[23]。由于该过程具有多步骤的特性，不同分化轮次之间也可能会产生变异性。为了解决这个问题，应当在可行的情况下跨多个独立分化批次和多个克隆（clones）进行数据收集，并在分析过程中将分化批次纳入考量。

来自其他基于 iPSC 研究领域的启示表明，遗传背景是重新编程后 iPSC 细胞系之间变异性的主要来源[24,53]。在模拟特发性（idiopathic）或环境驱动的疼痛疾病，例如化疗致周围神经病变时，这一考量尤为重要。在此类病例中，实验组应当包含源自多个供体的 iPSC 细胞系，而不是依赖于单一细胞系的重复测量。转录组学分析表明，各组通常需要四到六个独立的细胞系，尽管适当的样本量应当由模型特异性的功效分析（power analysis）来决定[13,18,29]。在单基因疼痛障碍（如 Nav1.7 通道病变）的情况下，使用同源基因对照（isogenic controls）提供了一种控制遗传背景的有效策略，前提是必须进行严格的质量控制，以排除基因组编辑的脱靶效应（off-target effects）。

除了实验设计之外，准确且一致地报告实验参数对于方法学上的严谨性至关重要。标准化的报告框架，例如 RIVER 建议（RIVER Recommendations）[57]、FAIR 准则[59] 以及 ENTRUST PE 框架[16]，为透明的文献记录提供了切实可行的指导，并被强烈建议用于提高跨实验室神经病理性疼痛模型的可复制性。

结论与展望 (Conclusion and Outlook)

本情况说明总结了目前用于研究干细胞来源的神经病理性疼痛模型的现有方法与概念，旨在为疼痛研究人员与干细胞研究领域内的现有资源之间搭建桥梁。

尽管 iSN 模型在过去十年中不断得到优化，并已成功用于阐明病理机制与患者特异性的表型，但一些局限性与挑战依然存在：我们的培养系统中缺乏感觉神经元的天然微环境（natural niche）、需要延长的成熟时间，以及在涉及某些疼痛靶点（例如 TRPV1 和 Nav1.9）时，iSNs 与原代背根神经节（primary hDRG）神经元相比功能性有所降低。优化的培养条件和分化范式应当有助于克服这些障碍。近年来，更复杂的培养系统数量有所增加，包括人类 iSNs 与主要或 iPSC 衍生的施万细胞（Schwann cells）或卫星胶质细胞（satellite glial cells）的共培养[4,8,22,30,54]、iPSC 来源的背根神经节类器官（dorsal root ganglion organoids）[34,35]，以及重构躯体感觉通路的多个神经元类器官组装体（assembloids）[25]。在我们的研究领域内开发并应用严谨的方法，以及公开报告和共享分化与培养方案，将有助于进一步改善我们的模型系统与研究，使我们更接近于更好地理解周邊神经元的发育、功能和病理学。

资源 (Resource)

https://youtu.be/iFfjQ5k7hqo?si=5b0y2wiiWNHGoV6g 观看一段 由 Pascal Röderer 博士主讲的8 分钟视频，该视频详细介绍了在神经病理性疼痛研究背景下，使用诱导性多能干细胞（iPSC）衍生模型的核心资源、分化策略以及实用技巧。

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资讯披露 (Disclosures)

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