

# 框架核酸在原位成像中的应用：技术进展与未来展望

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## 摘 要

框架核酸(Framework Nucleic Acids, FNAs)作为一类新型纳米材料, 凭借其精确的结构与可编程设计的特性, 近年来在生物医学成像领域受到了广泛关注。FNAs兼具结构稳定性、生物相容性及功能可调性等独特优势, 使其在原位成像领域展现出广阔应用前景, 尤其适用于细胞表面标记、细胞内分子成像及活体生物成像等关键场景。尽管相关研究已取得重要进展, 但基于FNAs的成像技术仍面临稳定性不足、成像精度有待提升及应用范围较窄等挑战。因此, 本文系统总结了FNAs的设计原理、功能化修饰策略及其在原位成像中的多样化应用, 并展望了该领域未来的发展方向, 旨在为相关研究提供理论支撑与技术参考, 进而促进FNAs在生物医学成像领域创新发展。

## 关键词

框架核酸, 原位成像, 功能化修饰, 分子探针, 生物成像

# Framework Nucleic Acids for *In Situ* Imaging: Technical Advances and Future Prospects

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## Abstract

Framework Nucleic Acids (FNAs), as an emerging class of nanomaterials, have garnered significant attention in the field of biomedical imaging in recent years due to their precisely engineered structures and programmable design capabilities. FNAs exhibit distinct advantages—including structural stability, biocompatibility, and functional tunability—which render them highly promising for *in situ* imaging applications, particularly in critical scenarios such as cell surface labeling, intracellular molecular imaging, and *in vivo* biological imaging. Despite substantial progress in this area, FNA-based imaging technologies still face challenges including insufficient stability, suboptimal imaging precision, and limited application scope. Accordingly, this review systematically summarizes the design principles, functional modification strategies, and diverse applications of FNAs in *in situ* imaging, and discusses future directions for development in this field. The goal is to provide theoretical support and technical references for related research, thereby facilitating the innovative advancement of FNAs in biomedical imaging.

## Keywords

Framework Nucleic Acids, *In Situ* Imaging, Functional Modification, Molecular Probes, Bioimaging

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## 1. 引言

FNAs 是一种新兴的纳米材料，依托精确的三维结构、高度可编程性及理想的生物相容性，近年来在细胞成像、分子探针构建及靶向治疗领域均展现出卓越的应用潜力[1][2]。随着生物医学成像技术不断发展，原位成像技术已成为探究细胞和组织动态变化的关键工具，这种技术能实时观测生物体内生理过程，为疾病早期诊断与个性化治疗提供关键支撑[3][4]。传统成像探针或多或少存在稳定性差、靶向效果欠佳、生物相容性不好等缺点；而 FNAs 凭借其优异的物理化学特性，为解决上述瓶颈提供了新的思路与方法。

现有研究表明，FNAs 在细胞表面标记、细胞内成像以及活体成像领域已显露独特优势[5][6]，但仍面临分辨率低、信号稳定性差等问题。如何提高 FNAs 的成像信号强度、延长其在生物体内的留存时间、实现多种功能整合，已成为当前研究的重点[7][8]。未来，通过优化 FNAs 的合成方法与功能化策略，其在生物医学成像中的应用将更加广泛，有望成为疾病早期诊断与个性化治疗提供更精准的解决方案。

## 2. FNAs 的基础特性：结构、种类与核心功能

### 2.1. FNAs 的结构设计原则

FNAs 的设计以核酸链碱基配对为核心基础，通过精确控制核酸序列，达成多种空间构象的改变。利用 DNA 的自组装特性，可构建复杂的三维纳米结构，完成对目标的准确识别[9]。碱基配对方式与序列选择不仅影响 FNAs 的构象，还直接决定其成像性能，因此设计过程中应当充分平衡空间构象与功能实现的协同性。尺寸、形状和刚性是影响 FNAs 成像性能的关键要素：尺寸较大的 FNAs 细胞穿透性较差，而尺寸过小的 FNAs 易导致靶向能力不足[10]；刚性较大的结构在体内更稳固，但会限制细胞内变形能力，柔性结构虽有利于穿透细胞膜，但易受环境变化影响失去稳定性。因此，FNAs 设计需在尺寸、形状

和刚性之间寻求平衡，以确保其生物相容性和成像性能。

计算机辅助设计软件(如 oxDNA、CanDo 等)可模拟 FNAs 在不同条件下的构象变化，预测其在生物系统中的行为。通过分子动力学模拟，可评估 FNAs 在细胞环境与目标分子的相互作用，进而优化设计参数，提升成像的灵敏度与特异性[11]，计算机辅助设计工具使得 FNAs 的结构设计更为高效，加速其在生物医学成像领域的应用进程。

## 2.2. 合成技术与组装策略

FNAs 的合成方法主要包括自组合法、模板辅助法与酶促合成技术。自组合法利用氢键、静电及疏水作用驱动单链 DNA 自发折叠，操作简便且适于大规模制备，DNA 折纸为其典型应用[12]；模板辅助法通过预设 DNA 模板引导功能单元精确排布，实现对产物结构与性能的程序化调控[13]；酶促合成法借助核酸酶催化合成复杂结构，可提升产率及环境敏感性结构的稳定性[14]。

组装过程受温度、离子强度及链浓度协同调控：适度升温可加速分子碰撞与组装，但过高易致变性解链[15]；适宜盐浓度可屏蔽静电斥力促进特异性杂交，过高则诱导沉淀或失活[16]；提高链浓度可增强分子相互作用、提升组装效率，但过高易引发聚集体、破坏产物均一性[17][18]。因此，FNAs 的高效合成与稳定组装需对上述参数进行系统优化。

## 2.3. 主要种类及结构特征

根据几何构型，FNAs 可分为一维、二维及三维结构。一维 FNAs (如 DNA 纳米管)呈线状或管状，可作为分子导线定向排布纳米材料；二维 FNAs (如二维晶格)具有明确的平面边界，可作为分子画布实现蛋白质、抗体等生物分子的精确排布，适用于生物传感与细胞界面研究；三维 FNAs 具备立体空间构型，是当前生物医学应用的重点，其代表性结构包括柏拉图多面体(如 DNA 四面体、八面体、十二面体)及复杂三维折纸结构(如 DNA 盒子、笼、球)，可作为纳米容器封装药物或作为功能分子定位支架[19]。

## 2.4. 核心功能特性

### 2.4.1. 结构可编程性

FNAs 的结构可编程性源于 DNA 碱基互补配对原则，通过设计“订书钉”链引导长链模板折叠，可精确构建预设的二维或三维纳米结构[20]-[22]。该特性主要体现在两方面：其一，几何构型可设计——通过预测并优化序列折叠路径，可形成多面体、纳米管、纳米笼等复杂结构；例如以六螺旋束为基本单元，可进一步组装为八面体、立方体等高对称性三维超结构[23]-[25]。其二，动态响应可编程——通过引入可逆化学键或光敏基团，可赋予 FNAs 外界刺激响应能力，如紫外光触发光敏保护 DNA 解离，驱动构象重构[26][27]。上述特性使 FNAs 在生物医学、材料科学及分子计算等领域展现出广阔应用前景。

### 2.4.2. 生物相容性与稳定性

生物相容性和稳定性是 FNAs 在生物医学应用中关键特性。其一，FNAs 多由天然核酸合成，显著降低免疫原性，具备良好的生物相容性[5]。其二，经过化学修饰，可增强 FNAs 抵抗核酸酶的能力，延长 FNAs 在生物体内的半衰期，提升靶向药物递送效果。此外，环境响应性的结构设计能让 FNAs 根据外部刺激(pH、温度等)调节自身功能，为动态生物环境中的应用提供新途径。基于上述特性，FNAs 可广泛应用于基础研究与临床治疗，为生物医学领域提供安全、高效的技术工具。

### 2.4.3. 表面功能化能力

FNAs 的表面功能化特性在生物医学领域中应用广泛，通过精确修饰表面位点可显著提升其与靶标分子的结合力，该特性在靶向药物递送和生物传感器设计中尤为关键。例如，在 FNAs 表面修饰多价配

体,可显著提升其表面的结合能力,提高细胞识别与靶向治疗中的效果;同时,在 FNAs 表面修饰荧光基团与报告分子,可实时监控生物过程,为生物成像和临床检测提供技术支撑[6]。多样化的表面功能化策略使 FNAs 的应用前景宽阔,通过不同表面功能化策略,可发挥 FNAs 在细胞识别与药物递送方面的作用,为其在生物医学领域的深度应用奠定基础。

#### 2.4.4. 跨膜递送能力

FNAs 通过自组装形成高度有序的纳米结构,可精确控制尺寸、形状与表面功能,为跨膜递送提供了理想的平台。其核心优势在于模块化设计,经由简单的调整序列就可实现多功能整合,承载药物、核酸或其他生物大分子,并借助特定的跨膜机制将这些分子送入目标细胞内部[28]-[30]。FNAs 与细胞膜的相互作用机制多样。首先, FNAs 可通过表面功能化来模拟病毒膜融合,在细胞膜上形成临时孔隙,促进负载分子跨膜转运。有研究表明,将膜融合肽应用在 FNAs 表面,可诱导细胞膜局部融合,实现高效跨膜传递[31]。其次, FNAs 还可通过设计特定的表面电荷分布,提升其与细胞膜间的静电相互作用,推动跨膜传递[32]。另外, FNAs 能携带相关免疫分子参与免疫调节,激活或抑制特定免疫反应,为免疫治疗增添新的方向[33]。

### 3. FNAs 在原位成像中的应用

#### 3.1. 细胞表面标记应用

FNAs 凭借其几何结构可编程性与多价配体精准排布能力,在细胞表面受体识别标记中展现出独特优势,尤其适用于多受体协同识别。Yao Hong 等利用 DNA-肽杂交探针实现 FNAs 对特定受体对的双特异性识别,显著提升细胞亚型鉴别能力与内吞效率[34]。Xiaoxue Hu 等进一步以 10 种适配体对 12 种细胞系进行表面受体分析,证实适配体种类、价态及几何排布的精确调控可增强多异受体介导的识别特异性,并通过促进网格蛋白依赖内吞显著提高细胞摄取效率[35]。Xingyu Chen 等通过耗散粒子动力学模拟揭示, tFNAs 的柔韧性及拓扑结构直接影响其膜结合效率与内化行为[36]。此外, FNAs 还可整合多功能模块构建诊疗一体化平台。Jie An 等将  $^{131}\text{I}$  标记多柔比星负载于免疫分子修饰的金属有机框架 MIL-100 (Fe),借助 FNAs 对肿瘤受体的高效识别,实现靶向药物递送与治疗进程的实时成像监测,为提升临床治疗的可控性与安全性提供了新策略[37] [38]。

#### 3.2. 细胞内成像应用

FNAs 因其高度程序化的结构设计能力和良好的生物相容性,在细胞内成像领域展现出巨大的应用潜力。随着成像技术和探针设计的不断进步,基于 FNAs 的成像方法在提高成像灵敏度、空间分辨率及生物稳定性等方面取得了显著进展。

以荧光显微镜为代表的传统细胞内成像技术依赖于特异性荧光标记物对靶分子进行标记,然而,荧光探针常受光漂白和信号扩散的限制[39]。针对这一问题,研究者开发了多种基于 FNAs 的纳米探针,如荧光碳点[40]、DNA 纳米结构辅助的 FRET 纳米探针[41]以及 DNAzyme 放大平台[42],通过精确设计核酸序列和结构,实现对细胞内 RNA、离子和蛋白质等靶标的高灵敏度、高选择性时空动态监测。例如:为减少细胞毒性和非特异性干扰, tFNAs 因其尺寸适中和结构稳定性,被广泛用于细胞内递送和成像[43]。此外, FNAs 能够与多种功能分子(如荧光团、磁共振成像对比剂等)共价连接,构建多模态成像平台,提高成像的通量和信息维度[44] [45]。Peng Gao 团队报道了一种智能核酸门控的共价有机框架纳米系统:利用 Cy5 染料标记单链 DNA 吸附于载有阿霉素的共价有机框架纳米颗粒表面,通过过表达的 TK1 mRNA 可触发单链 DNA 解离,从而恢复 Cy5 的强荧光信号的同时,释放负载的阿霉素,实现化疗[46]。

先进的成像技术与 FNAs 结合也推动了细胞内成像能力的跃升。高光谱成像技术和干涉散射显微镜(iSCAT)能实现纳米尺度细胞内结构无标记高速成像,为揭示细胞内物质运输和蛋白复合物动态监测提供新视角[47][48]。Xingjie Hu 等人针对活细胞中分层 FNAs 的行为和调控机制研究,构建了一个具有五个四面体 DNA 纳米笼的树突状纳米结构。他们发现与 FNA 单体相比, FNAs 树枝状聚合物表现出更强的胞吞作用和更长的细胞滞留时间,从而证明 FNAs 及其高阶衍生物是理想的细胞内成像探针和纳米载体[49]。

### 3.3. FNAs 的功能化修饰策略及其对成像性能的影响

近年来,通过在框架核酸(FNAs)上进行精确荧光标记,成像灵敏度与信噪比显著增强,并催生了多元化的成像应用。Xue Hu 等组装了 DNA 立方体核心,并在此基础上位点特异性地同时修饰两种发夹探针(H1 和 H2),构建了价态可调(一至八价)的同质/异质传感平台。通过固定一种探针数量、系统改变另一种,首次在分子水平证明:调控 DNA 链价态可优化荧光响应性能,进而提升生物传感的灵敏度与动态范围[50]。

结合多级核酸扩增策略可进一步提高成像灵敏度。Hao Jiang 等将滚环扩增(RCA)与 FNAs 级联,结合侧流测定(LFA)实现了 miRNA let-7a 的灵敏检测,检出限达 1.07 pM,灵敏度较 RCA-LFA 提高近 20 倍;且 HCR 非目标依赖性自组装不占用检测时间,较传统级联方法更为高效[51]。

靶向配体修饰是 FNAs 功能化的另一重要策略——通过构建与细胞表面受体高亲和力结合的核酸配体复合物,实现精准识别与选择性成像[52][53]。多价适配体设计可显著增强结合亲和力与靶向效率。Pritam Ghosh 等利用两种肽类靶向配体,在实现细胞毒性载荷特异性靶向与内化的同时,构建了细胞独特指纹识别系统[34]。此外,抗体及其片段亦可作为高亲和力靶向分子修饰 FNAs 表面。Naoya Kato 团队通过 Fc 区对脂质纳米颗粒进行抗体定向修饰,优化间隔肽后显著提升了荧光素酶蛋白表达量;该策略在避免传统随机偶联所致识别效率下降的同时,保证了靶向分子的功能性与稳定性[54]。

## 4. FNAs 成像的技术优势和挑战

FNAs 在生物成像领域展现出革命性潜力,其核心优势包括:纳米级空间分辨率——借助可编程结构与精准定位能力,结合光化学去保护等信号增强策略,实现高信噪比、高特异性的亚细胞定位成像;多重编码能力——通过组合荧光标记与核酸适配体,可在单次实验中实现多种靶标的高维同步成像,显著提升研究通量[55];动态响应性能——结构柔性与环境适应性使其支持高时间分辨率成像,适用于捕捉细胞内信号的瞬时变化[56]。

然而,其临床转化仍面临多重挑战:体内稳定性不足,核酸酶介导的快速降解严重制约活体应用[57];规模化制备瓶颈,合成工艺复杂、质控难度高,成本与批次重现性问题尚未解决[58];生物环境干扰,离子浓度、pH 及分子竞争等因素影响成像信噪比与结果稳健性,亟需优化探针设计与信号淬灭策略。此外,标准化与智能分析体系缺失:信号强度校准方法缺乏统一基准,数据跨实验可比性差;面向海量成像数据的智能解析算法尚短缺,制约定量分析能力[59][60]。

## 5. 总结和展望

过去二十年,框架核酸(FNAs)凭借其结构可编程性、稳定性与功能化能力,在细胞表面标记、细胞内成像及活体成像中展现出优异性能与广阔前景。本文从 FNAs 的结构特征、分类与核心功能出发,系统综述近十年研究进展。尽管学者们在结构设计、功能修饰及应用拓展方面取得显著突破,并预期未来将向智能设计、多技术融合与临床转化持续演进,但 FNAs 成像探针的临床转化仍受制于两大工程化瓶

颈，而非基础结构创新。

其一，大动物安全性评价数据系统性缺失。现有活体毒理研究全部局限于啮齿类动物(BALB/c、SJL/J小鼠)，仅能证实单次静脉给药在 4 mg/kg 剂量范围内无急性毒性及特异性抗体应答[61]；然而，其肝蓄积与肾清除特征能否在非人灵长类中复现、人类免疫通路激活阈值是否与小鼠相当，迄今未见任何实验报道。任何进入临床申报的核酸纳米制剂均需提供啮齿类与非啮齿类动物重复给药毒性数据，而猪、犬或猴的相关药代动力学、免疫原性及组织蓄积毒性研究完全空白，直接导致 FNAs 成像制剂被阻断于 IND 申报门外。其二，规模化制备中批次一致性控制体系尚未建立。绝大多数 DNA 折纸结构仅公开寡核苷酸序列，而缺失可编辑的高维度设计文件(如 caDNAno 源文件)，致使工艺优化无法迭代、关键质量属性无法追溯。规模放大时，大体积退火温度梯度易致构象异质性[62]，PEG 沉淀或切胶回收在毫克级以上制备中回收率常低于 30%；多位点定点修饰在大反应体系中副产物比例骤升、特异性显著下降，致使荧光强度、靶向亲和力及血清半衰期等核心性能沦为批次的函数，重现性丧失。

上述困境的本质是领域内“工程思维”的系统性缺位——近二十年数以千计的研究持续驱动结构拓扑创新与应用场景拓展，却极少将资源投入至工艺放大、质量控制及大动物安评等决定转化成败的关键环节。未来 FNAs 若要在原位生物医学成像领域实现临床落地，研究重心必须从“演示新型探针”转向“建立工程化验证范式”：尽快启动非人灵长类重复给药毒性实验、构建开源可编辑的设计文件库、开发连续流退火与位点特异性修饰的规模化工艺。唯有填补上述转化断层，方能将“小鼠图像”转化为“临床诊断工具”。

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