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Vault Organelles: Structure, Mystery, and Emerging Insights

Introduction and Background

Vaults are large barrel-shaped ribonucleoprotein particles found in the cytoplasm of many eukaryotic cells [1]. They were first discovered in 1986 by Nancy Kedersha and Leonard Rome, who noticed unusual dome-shaped particles while purifying cell vesicles [2]. The particles were named **vaults** for their resemblance to cathedral vaulted ceilings [3]. At about 70 nm in length and 35 nm in width, vaults are roughly three times the size of a ribosome and have a mass around 12–13 MDa [4] [5]. **Figure 1** shows a cryo-electron microscopy image of human vault particles alongside a 3D density map, illustrating the hollow, barrel-like shape of these organelles. Vaults consist of two identical half-shells that can open and close, giving them a distinct capsule-like morphology. Notably, vault particles exhibit a **39-fold radial symmetry** (denoted as D_39) when viewed down their long axis [6]. This unusual symmetry contributes to their striking appearance under the electron microscope, akin to ornate vaults or half-barrels.

Figure 1: Cryo-EM visualization of human vault particles. (A) Electron cryo-micrograph of vaults (pink arrows) in a cell extract, alongside other cell components (green arrows indicate contaminant filaments; orange arrows indicate ferritin). (B) Reconstructed 3D density map of the vault, revealing its barrel-shaped, hollow structure (~35 nm diameter by ~70 nm length) [7].

Vaults are composed of a relatively simple set of components despite their large size. **Major Vault Protein (MVP)** is the predominant building block: ~96–100 kDa in size, and present in 78 copies per vault, forming the vault's outer shell [8]. MVP monomers assemble into the vault wall in a head-to-head fashion, with their N-termini meeting at the vault's midsection (the "waist") [9]. In addition to MVP, vaults contain two smaller proteins in much lower copy number: **VPARP** (vault poly(ADP-ribose) polymerase, also known as PARP4, ~193 kDa) and **TEP1** (telomerase-associated protein 1, ~240–290 kDa) [10]. Early biochemical estimates suggested each vault particle includes roughly eight copies of VPARP and two copies of TEP1 [11]. These minor vault proteins reside in the vault interior and attach to the MVP shell: for example, VPARP binds to a central repeat domain of MVP, while TEP1 (a WD-repeat protein) binds near the vault's cap region [12] [13]. Vaults also harbor small untranslated RNAs known as **vault RNAs (vRNAs or vtRNAs)**, typically 86–141 nucleotides long [14]. Each vault particle usually contains a few copies of vRNA (at least 6 per vault in some estimates) that localize near the end caps of the vault [11] [15]. These RNAs are transcribed by RNA polymerase III and are not thought to contribute to the vault's structural integrity, but instead are believed to play regulatory roles [15]. In summary, the vault is built from one major shell protein, two auxiliary proteins, and several small RNAs – a simplicity that contrasts with its massive size. This minimal composition (just three protein types) led one commentator to note that vaults "are larger than a ribosome, yet also simple – containing just three different proteins where a ribosome might contain a hundred" [5].

Vault particles are strikingly **conserved across eukaryotic evolution**. MVP homologs have been identified in a wide range of organisms: mammals (human, rodent, cow), birds, amphibians, fish, mollusks, and even protozoans [16]. Comparative genomics suggests MVP was already present in the last eukaryotic common ancestor (LECA) [17]. In species that have vaults, they are often extremely abundant: a typical human cell contains on the order of 10,000 vault particles [18], meaning an average

human body may carry *10^14–10^17* vaults in total [19]. However, vaults are not universal to all eukaryotes. Notably, large groups like fungi, nematodes, and arthropods lack an MVP gene entirely [20]. Classic model organisms such as *Saccharomyces cerevisiae* (yeast), *Caenorhabditis elegans* (roundworm), and *Drosophila melanogaster* (fruit fly) do not have vaults [20] [21]. This patchy distribution implies that vaults were lost in certain evolutionary lineages – possibly those species found alternative solutions for whatever function vaults served. Intriguingly, even the slime mold *Dictyostelium* has been reported to form only **half-vault** structures, which might reflect a species-specific adaptation [22]. Overall, wherever vaults are present, their sequence and structure are highly conserved, underscoring that they likely confer important advantages to the organisms that retain them [10] [16]. Yet despite this conservation and abundance, the biological purpose of vault organelles has remained elusive for nearly four decades.

Structural Architecture and New Cryo-EM Insights

Structurally, vaults are hollow nanocapsules with two identical halves that join at a central "waist." Each half-vault is composed of 39 MVP subunits arranged in a curved, arched lattice. When the halves come together, the whole vault exhibits a **39-fold dihedral symmetry** (D_39) around its longitudinal axis [6]. Earlier electron microscopy studies measured vault dimensions as roughly 35–40 nm in diameter and 65–70 nm in length [4]. High-resolution analysis reveals that MVP's tertiary structure consists of multiple repeated domains that trace the contour of the vault's barrel: nine alpha-helical repeats forming the vault's body, a "shoulder" domain, and at the tip, a **cap domain** that includes a helix-loop structure and a ring-like motif [9]. The N-terminal domain of MVP (repeat R1) lies at the vault's midsection, mediating the interaction of the two halves, whereas the C-terminal cap region of MVP forms the vault's closed ends [9]. The minor vault components interact with specific MVP domains: VPARP attaches to one of the internal repeats of MVP (repeat #4), and TEP1 binds near the cap, where it also associates with a vault RNA packed into that end of the particle [9]. These arrangements hint that the vault's ends might be specialized for controlling access to its interior—perhaps gating the entry and exit of molecules.

Until recently, structural knowledge of vaults came from moderate-resolution techniques (around 9 Å cryo-EM and X-ray crystallography of portions of MVP). In 2025, however, a breakthrough came from a **high-resolution cryo-electron microscopy** study of human vaults by Lövestam and Scheres [23]. This work, exploiting vault particles serendipitously found in human brain tissue, achieved ~3.1 Å overall resolution and illuminated previously unseen details [24] [25]. Most strikingly, the new structure revealed a **symmetry mismatch at the vault's end caps** [26]. Whereas the central barrel of the vault retains 39-fold symmetry, the researchers discovered that at the very tip of each cap the symmetry reduces to 13-fold. In other words, only *13 MVP monomers (out of the 39 in a ring)* continue to form the final cap structure, while the other two-thirds of the subunits peel away sequentially before reaching the apex [27] [28]. This finding means that the vault's closed end is not a uniform dome of 39 subunits, but rather a narrower structure – essentially a triangular arrangement of 13 subunits – leaving a small central **pore**. The pore is lined by hydrophobic residues (e.g. Leu381, Ile382 of MVP) forming a "greasy" ring around the opening [29]. Such a hydrophobic plug could make the vault cap less permeable to solvent, potentially keeping the interior isolated until specific conditions cause it to open. Notably, earlier reconstructions that imposed 39-fold symmetry had produced smeared, uninterpretable density at the caps [30] [31]. By using focused classification without imposing full symmetry, Lövestam and Scheres resolved three distinct cap conformations corresponding to which MVP monomers are excluded, confirming the 3×13 arrangement [26] [32]. This symmetry-mismatch mechanism explains how vaults taper to a closed tip and provides clues to how they might open: presumably, some trigger could allow the excluded subunits to rearrange or the 13-mer cap to disassemble, creating an aperture.

These new structural insights refine our understanding of vault assembly and suggest ways to **engineer vaults for biotechnology**. The 2025 study noted that the C-terminal ~90 amino acids of MVP (which form the cap ring) were flexible and unresolved in the symmetric vault structure [30] [33], but became ordered in the 13-fold symmetric cap reconstruction. This region of MVP can likely tolerate modifications or insertions – indeed, it has been a target for adding peptides in engineered vault nanoparticles. The observation of a narrow, hydrophobic pore at the vault's tips raises the possibility that vaults might normally permit small molecules to diffuse when open, or conversely, that they maintain a sealed compartment until a specific signal (e.g. a pH drop or binding event) triggers cap opening. Lövestam and Scheres remarked that understanding the cap architecture offers "valuable insights for engineering carboxy-terminal modifications of MVP for potential therapeutic applications" [34]. In practical terms, this could mean designing vault particles that open on cue or that present functional peptides on their tips. Prior to this cryo-EM work, vaults were sometimes described as "vault-like" or "clam shell" particles that might hinge open. Now, with near-atomic detail, we have a clearer picture: vaults contain a built-in **mismatch mechanism** that naturally creates a closed vault with a latent opening at each end [35] [36]. This discovery is a significant step toward unlocking how vaults load or release cargo – a key piece of the vault puzzle.

The Vault Paradox: High Abundance but Non-Essential?

One of the biggest mysteries surrounding vaults is the disconnect between their prevalence and their apparent dispensability. Vault components are highly conserved and often *very* abundant (MVP is among the most common cytoplasmic proteins in some cells [37]), yet laboratory knockouts of vault genes produce surprisingly mild phenotypes. For example, mice lacking MVP (the main vault protein) develop normally, are fertile, and show no obvious anatomical or developmental defects [38]. These MVP-knockout mice have intact immune cell function and essentially normal physiology, apart from subtle changes under specific challenges [39]. Likewise, knockout of TEP1 in mice ablates the association of vRNA with vaults, but otherwise the vault particles still assemble (without RNA) and the mice are viable and healthy [40]. Even removing VPARP (PARP4) did not yield a dramatic phenotype in mouse models [41]. In short, eliminating one or even multiple vault components in model organisms does not result in lethality or any overt syndrome – suggesting vaults are **not strictly essential** for basic viability, at least under laboratory conditions. This perplexing result stands in contrast to how conserved vaults are: evolution usually *does not* retain a 13-megadalton complex for billions of years without a good reason.

How can we reconcile these facts? One interpretation is that vaults provide a **non-essential but advantageous function** that becomes important only in particular contexts – for example, under environmental stress, disease conditions, or in long-term organismal fitness. In a sterile lab environment, animals might not encounter the specific challenges that vaults evolved to address. Indeed, vaults have been proposed to act in processes like xenobiotic resistance, immune defense, or stress tolerance (discussed below), which might not be triggered during routine husbandry of lab mice. There may also be redundancy: other cellular systems could compensate when vaults are absent. It's telling that species which entirely lack vaults (yeast, flies, etc.) are not obviously handicapped; presumably, those lineages evolved alternate mechanisms to fulfill any roles vaults played. Conversely, the fact that many complex organisms *do* maintain vaults suggests those organisms benefited from vault-mediated functions in their natural ecology or during evolution. In human cells, MVP is known to be upregulated in certain circumstances (for instance, in drug-resistant cancer cells or in response to interferon signaling), hinting that vaults might be part of inducible adaptive programs [42] [43].

Another facet of this paradox is that vault components can be lost with minimal immediate consequence, yet subtle phenotypes are starting to emerge upon closer scrutiny. For example, MVP-knockout mice, while healthy overall, show altered responses to certain stresses: some studies noted

changes in their immune signaling or susceptibility to infections and toxins, suggesting vaults modulate these responses in a way that isn't obvious until challenged [43] [44]. Similarly, cells without NSUN2 methyltransferase (affecting vault RNA, see below) appear normal at a glance but have hidden dysregulation of small RNAs that only manifest in specific tissues or under stress [45] [46]. These observations imply that vaults might function as a **cellular "insurance policy" or stress-response reserve** – not required for everyday growth, but crucial for optimal performance during physiological stress, infection, or environmental change. This idea aligns with vaults' high copy number: a cell stockpiling thousands of vault particles might be preparing for a rapid response to some eventual challenge (like a cache of tools ready to be deployed when needed). The challenge for researchers is to identify those conditions under which vaults become indispensable. The coming sections review leading hypotheses about what vaults *might* be doing in cells, setting the stage for a unified view of their role.

Proposed Biological Functions of Vaults

Given their mysterious nature, vaults have attracted many hypotheses regarding their function. While none of these models has been definitively proven, each is supported by certain observations. A consensus is emerging that vaults may be multifunctional – acting in several pathways such as transport, signaling, and defense. Key proposed roles include:

1. **Nucleocytoplasmic Transport:** Vaults have long been suspected to shuttle molecules between the nucleus and cytoplasm. They are often found near nuclear pore complexes, and their overall size and eightfold-symmetric "barrel" shape loosely resemble the nuclear pore architecture [47]. Early cell studies showed vaults at the nuclear envelope, hinting at transport activity [48]. Moreover, the vault complex can redistribute rapidly in response to stress and has been hypothesized to facilitate exchange of proteins and RNA between the cytoplasm and nucleus [49]. For instance, vaults might carry specific RNAs or signaling proteins into the nucleus under certain conditions, or ferry newly exported RNAs out to the cytosol. This idea remains under investigation, but it is supported by the discovery that vault-related proteins can influence nuclear localization of factors like PTEN (a phosphatase) in a calcium-dependent manner [50] [51]. Thus, vaults could serve as **mobile transport pods**, augmenting the classical nuclear transport system for select cargoes.

2. **Multidrug Resistance and Detoxification:** Vaults have been implicated in cellular defense against toxins and drugs. MVP was originally identified in cancer cells as **"lung resistance protein" (LRP)**, correlated with poor response to chemotherapy [10]. Vault levels (especially MVP and vtRNA) tend to be higher in multi-drug-resistant tumor cell lines, and reducing vault RNA can resensitize cells to drugs [52] [53]. One proposed mechanism is that vaults bind or sequester drugs and help eject them from cells – essentially acting as a **chemo-resistance factor**. For example, vault-associated RNAs have specific binding sites for chemotherapeutic compounds and may facilitate their export or sequestration [54] [55]. In one study, cancer cells with high vtRNA levels were resistant to the drug mitoxantrone, whereas cells with silenced vtRNA became more drug-sensitive [56]. It's also possible vaults indirectly affect drug resistance by regulating gene expression (via vtRNAs, see below) or interacting with drug transporters. In an evolutionary sense, vaults might function in detoxification of harmful substances – an ancient role that could explain why organisms retained them for millions of years [57]. Encapsulating and isolating toxins in a protein vault could protect vital cellular machinery, analogous to how vaults have been used to carry drugs in nanotechnology. Thus, vaults may be the cell's internal **detox vaults**, contributing to multidrug resistance and chemical stress protection.

3. **mRNA Localization and Storage:** Some researchers speculate that vaults participate in localizing mRNAs or temporarily storing them ("vaulting" them) until needed. Vaults are RNPs with a roomy interior, so they could, in theory, package specific messenger RNAs and traffic them to particular regions of the cell. There is evidence that vault particles can **relocate within the cell in response to stimuli**, which might redistribute mRNAs or proteins bound to vaults [49]. Additionally, TEP1 (a vault component) was first identified through its association with telomerase RNA, suggesting vaults can bind other RNPs [12]. It has been proposed that vaults might carry certain transcripts (for example, mRNAs needed for cell migration or localized protein synthesis) and release them at the right time and place. Another possibility is that vaults store mRNAs during cellular quiescence or stress and release them when conditions improve, thus controlling the timing of protein production. While direct proof is still lacking, such a **"vault as mRNP shuttle"** model aligns with vaults' ability to encapsulate RNA and their dynamic cellular localization.

4. **Innate Immunity and Viral Defense:** Emerging data suggest vaults, particularly vault RNAs, play a role in the immune system. A prime example is **vtRNA2-1 (also called nc886)**, which can bind to the antiviral protein kinase PKR. PKR is an innate immune sensor of double-stranded RNA that, when activated, shuts down protein synthesis to combat viruses. Vault RNA 2-1 contains a double-stranded region that binds PKR and keeps it in an inactive state [58]. By acting as a decoy or inhibitor, vtRNA2-1 essentially **tones down PKR activity**, which can influence the cell's antiviral responses [59]. In fact, some viruses appear to exploit this: infection with influenza A virus strongly upregulates vault RNAs in host cells, which helps suppress PKR and allows the virus to replicate more efficiently [59]. On the other hand, vaults might aid the immune system in other ways. A recent idea is that vault particles themselves could function as **danger signals** when released from dying cells – the sudden appearance of free vaults in extracellular fluid might alert antigen-presenting cells (APCs) that cell damage has occurred [60]. Vault Pharma researchers noted that vaults are rapidly engulfed by macrophages and dendritic cells if spilled into the extracellular space, implying a role as an "eat me" signal or immune stimulant upon cell lysis [60]. Furthermore, MVP expression is induced by immune cytokines like interferon-γ, and MVP has been shown to interfere with interferon-mediated signaling pathways [43]. Taken together, these points suggest vaults intersect with the immune system both **intracellularly (via RNA-mediated regulation of antiviral pathways)** and **extracellularly (as potential signals or adjuvants)**, although much remains to be clarified.

5. **Cell Signaling Scaffold:** Beyond their RNA-related functions, vaults (especially MVP) have been found to interact with various signaling proteins, hinting at a role as a scaffold or modulator in signal transduction. One well-documented interaction is between MVP and the tumor suppressor **PTEN** – a critical phosphatase in the PI3K/Akt signaling pathway. MVP directly binds to PTEN's C2 domain and sequesters a fraction of PTEN in vault particles in the cytoplasm [61] [62]. This interaction is calcium-dependent and can influence PTEN's subcellular localization and activity [51] [63]. By holding PTEN in the cytosol, vaults might regulate how much PTEN enters the nucleus or membrane, thereby tuning cell growth and survival signals. MVP has also been reported to associate with other signaling hubs: for instance, it binds to focal adhesion kinase (FAK) and receptor tyrosine kinases like EGFR, and may modulate downstream ERK/MAPK signaling [64] [65]. In cancer cells, high MVP levels have been correlated with activation of pro-survival pathways (like STAT3 in lung cancer) or, conversely, MVP re-expression can sometimes suppress oncogenic signaling depending on context [66] [67]. These seemingly conflicting findings suggest MVP's effect on signaling is context-dependent, possibly serving as a **buffer or anchor for signaling proteins**. In some scenarios vaults might dampen signals by sequestering key players (as with PTEN), while in others they might assist in assembling signaling complexes. The idea of vaults as dynamic scaffolds could explain why they are so abundant: a single cell

might use thousands of vault particles to bind and compartmentalize signaling molecules, ensuring signals are properly modulated in space and time.

6. **"Cellular Cache" Hypothesis:** An overarching theory is that vaults serve as *general storage and sorting organelles* – essentially cellular vaults in the literal sense. In this view, vaults could pick up diverse cargos (RNAs, metabolites, enzymes) and keep them in a protected compartment until a trigger causes release or exchange of the contents. This would make vaults flexible multi-use containers. Some support for this comes from vaults' ability to encapsulate various materials (as seen in engineering experiments and the natural binding of different RNAs/proteins to vault components). Evolutionary analyses point out that while MVP is ancient, the other vault components (vRNA, VPARP, TEP1) may have been recruited later, suggesting the vault acquired new functions over time by adding new "contents" [17]. The retention of vaults in many lineages could be due to their usefulness as a platform for **encapsulation and detoxification** of harmful substances or as a reservoir for beneficial factors [57]. For example, vaults might isolate oxidative enzymes or sequester excess heme/iron to prevent damage, then release them when needed. Although direct evidence is sparse, this cache hypothesis synthesizes many observations: it accounts for vaults' large cavity and ability to hold cargo, their inducibility under stress, and their nonessential nature (serving as a reserve rather than a critical component). In effect, vaults could be the cell's version of a **Swiss army knife nanocapsule** – not always in active use, but capable of being deployed for various tasks such as transport, detox, or signaling when conditions demand.

It's important to note that these hypotheses are not mutually exclusive. Vaults might fulfill *multiple* roles, potentially in a cell-type-specific or condition-specific manner. For instance, in immune cells they might predominantly act in signaling or antigen processing, whereas in tumor cells they might lean toward drug resistance and gene regulation. The multifunctional nature of vaults could help explain why a clear single phenotype has been hard to pin down. As research advances, the challenge will be determining which of these functions are primary versus ancillary, and how vault activity is regulated in vivo.

Vault RNA and Small Vault RNAs: Hidden Regulators

A significant twist in the vault story has been the discovery that the small **vault RNAs (vRNAs)** are more than just passive passengers. These Pol III transcripts – there are four in humans (vRNA1-1, vRNA1-2, vRNA1-3, and vRNA2-1/nc886) – reside within vault particles but also exist free in the cell. Growing evidence shows vRNAs can be processed into even smaller regulatory RNAs and interact with cellular RNA silencing machinery. In fact, vault RNAs have been called "hidden gems" of RNA regulation [68]. Key findings include:

- **Processing by Dicer into svRNAs:** Full-length vault RNAs (~90–100 nt) can be cleaved by the endoribonuclease Dicer, yielding **small vault RNAs (svRNAs)** about 21–24 nucleotides in length [69]. These svRNAs resemble microRNAs in size and function. For example, human vault RNA1-2 can be diced to produce *svRNA1-2*, which associates with Argonaute 2 (Ago2) and accumulates in the nucleus [70]. This svRNA was shown to modulate the expression of multiple genes, particularly those encoding cell membrane and signaling proteins [70] [71]. Another study found that an svRNA derived from vault RNA1 binds to Ago and downregulates **CYP3A4**, a drug-metabolizing enzyme [69] [72]. These results demonstrate that vault RNAs can act as precursors to miRNA-like molecules that fine-tune gene expression. Intriguingly, vault-derived svRNAs may use a noncanonical biogenesis: in at least one case, a vault RNA fragment (called snc886-3p from

vRNA2-1) is generated by Dicer *without* requiring Drosha, indicating vault RNAs bypass the usual microRNA nuclear processing step [73].

- **Regulation by NSUN2 methylation:** The biogenesis of vault-derived small RNAs is tightly controlled. A pivotal discovery was that the RNA methyltransferase **NSUN2** modifies vault RNAs at specific cytosine residues (introducing 5-methylcytosine marks), and this modification *prevents* excessive processing of vRNAs into svRNAs [68] [74]. In cells lacking NSUN2, vault RNAs are no longer properly methylated and consequently get aberrantly cleaved into Argonaute-bound fragments [45] [74]. These fragments can function as microRNAs and potentially disrupt normal gene regulation. In one report, patient cells deficient in NSUN2 showed an accumulation of vault RNA–derived small RNAs, which were implicated in the neurological symptoms seen in NSUN2 mutation disorders [45] [46]. Thus, NSUN2 normally acts as a gatekeeper: by methylating vault RNAs, it **flags them for retention** as full-length RNAs, whereas loss of methylation sends vault RNAs down a degradation pathway that generates regulatory svRNAs [45] [75]. This elegant mechanism links vault particles to epitranscriptomic regulation – essentially coupling a cell's metabolic state (NSUN2 activity) to the production of vault-derived gene regulators.

- **Interactions with Argonaute and RISC:** Small vault RNAs (svRNAs) that are produced can load into the RNA-induced silencing complex (RISC) just like canonical microRNAs [76]. For instance, the 3′ fragment of vault RNA2-1 (known as vtRNA2-1 or nc886 fragment) associates with Ago2 at levels comparable to bona fide miRNAs [73]. Only small RNAs that successfully enter RISC are considered functional, so detection of vault svRNAs in RISC is strong evidence they act in gene silencing [76]. Targets of these svRNAs are being uncovered: one known target is the aforementioned CYP3A4 enzyme, and others include genes involved in cell proliferation and apoptosis [69] [71]. Vault RNAs may thereby exert wide-ranging effects by spawning multiple svRNAs that each target different mRNAs. Notably, vault RNA fragments have been proposed to contribute to cancer phenotypes – for example, changes in vault RNA expression or processing have been linked to cell adhesion, migration, and drug resistance in tumor cells [71] [77]. The balance between full-length vault RNAs and their svRNA products might influence whether a cell adopts a proliferative or quiescent state.

- **Vault RNA as a PKR modulator:** As discussed in the immune context, one particular vault RNA (vRNA2-1, nc886) has a separate role aside from being a miRNA precursor: it directly binds and inhibits **PKR**, the double-stranded RNA-activated protein kinase [58]. The apical stem-loop of vRNA2-1 contains a short double-stranded region that PKR recognizes and binds, but this binding does not activate PKR – instead, it keeps PKR in an inactive state [58]. Essentially, vtRNA2-1 acts as an endogenous PKR inhibitor, preventing inappropriate antiviral response in the absence of actual viral infection. This function links vault RNA to innate immune homeostasis. If vault RNA2-1 is downregulated or epigenetically silenced (as happens in some cancers), PKR can become hyperactive, leading to chronic low-level interferon responses or other cellular stress pathways [78] [79]. On the flip side, viruses like influenza ramp up vault RNA expression to suppress PKR and evade host defense [59]. This paints vault RNAs as a double-edged sword: they are guardians against unwarranted immune activation, but can be subverted by pathogens. Interestingly, vault RNAs themselves are subject to epigenetic regulation – e.g. the promoter of vault RNA1-3 can be methylated in certain leukemias, silencing its expression [80]. Such findings imply vault RNAs might function as tumor suppressors in some contexts (when expressed, they keep oncogenic pathways like PKR in check) or as oncogenes in others (when processed into svRNAs that downregulate tumor suppressor genes). The vault RNA network is thus an important part of the vault organelle's *functional repertoire*, connecting the vault particle to gene expression regulation, drug resistance, and immune signaling.

In summary, vault RNAs and their derivative small RNAs have emerged as key players that could explain some of vaults' mysterious roles. They provide a molecular pathway by which vaults could influence everything from **drug metabolism** (via svRNA targeting of enzymes) to **cell signaling** (via PKR and possibly other RNA-binding proteins). The interplay of NSUN2, Dicer, and Argonaute on vault RNAs is a beautiful example of cellular regulation: vault RNAs are kept inert until a particular signal (loss of methylation) triggers their conversion into active signals (svRNAs). This dynamic may allow vaults to function as a switch – silently present in large numbers, but capable of producing a flurry of regulatory RNAs when certain stress conditions occur. It also highlights that the vault organelle cannot be understood by protein components alone; its RNA content is equally crucial.

Vaults in the Spotlight: Cultural and Scientific Intrigue

For decades, vaults lurked in the background of cell biology – known to a small number of researchers but omitted from most textbooks. Recently, however, these organelles have captured the imagination of a broader audience, becoming something of a cause célèbre in discussions of biological mysteries. A vivid example is a viral post on social media (X, formerly Twitter) by user @dystopiabreaker in 2024, which proclaimed vaults as "the most enigmatic structure in cell biology" and marveled that *"for 40 years since its discovery, we still don't know why our cells make these behemoth particles"* [81]. The post highlighted the basic facts – that vaults are present in every cell, highly conserved, and massive (three times the mass of a ribosome) – and asked, essentially, *what are they for?* This message struck a chord, accumulating thousands of likes and shares, and spurring popular science articles about vaults. On Reddit, a discussion thread about vaults similarly summarized the astonishment: *"All we know is it's in every cell in our body, incredibly conserved throughout evolution, it is massive... and we still have no idea what it does"* [82]. Such public reactions underscore the vault's almost poetic mystique – a vault hidden in plain sight within our cells.

This surge of interest has been met with enthusiasm by scientists who have long studied vaults, as well as newcomers intrigued by the challenge. Interviews with vault researchers (such as Leonard Rome) have appeared in the Royal Society of Biology blog and other outlets, emphasizing the puzzle of vault function and the unusual history of their discovery [83] [84]. A recurring theme is frustration mixed with fascination: vaults tick all the boxes of an important organelle (size, conservation, abundance) yet have defied our attempts to ascribe them a clear purpose [83]. The public discussion has even speculated on wild ideas – from vaults being cellular "USB drives" for horizontal information transfer, to them being a remnant of ancient viruses – showcasing how enigmatic they appear even to imagination. While many of these fanciful ideas lack evidence, they reflect a healthy curiosity and the allure of unanswered questions in biology.

Importantly, the newfound spotlight on vaults is also stimulating scientific progress. Increased awareness can attract funding and bright minds to tackle the vault problem. It also fosters cross-disciplinary dialogue: for instance, biophysicists interested in large protein assemblies, immunologists, and RNA biologists are now comparing notes on vaults. The vault thus serves as a reminder that even within our cells, fundamental structures can remain mysterious well into the 21st century. As one science communicator aptly asked, *"What's in the vault?!"* [85]. This blend of cultural intrigue and scientific tenacity may finally lead to cracking the vault's code.

Biotechnological Applications and Synthetic Vaults

Ironically, even before we fully understand their natural function, vaults have proven extremely useful as nanoscale tools. Their stable, hollow barrel architecture makes them attractive as **drug delivery vehicles, vaccine platforms, and nanobiotechnology devices**. Researchers have capitalized on

several advantages of vault particles: they are uniform in size (~70 nm), biocompatible (made of human proteins, thus non-immunogenic in the body), and can be produced recombinantly in large quantities. Here are some notable biotechnological applications of engineered vaults:

- **Drug Delivery Nanocapsules:** Vaults can be loaded with therapeutic molecules and used to ferry drugs to specific cells or tissues. The internal cavity of a vault is spacious (~50 million Å^3) and can hold a variety of cargos [86] [87]. By genetically modifying MVP, scientists have created vaults that package drugs in a controllable way. One strategy involved fusing a 31-residue peptide from the hepatitis C virus (NS5A) to MVP's N-terminus; this peptide forms **amphipathic helices** inside the vault, creating lipophilic rings that can bind hydrophobic drugs tightly [88]. Such vaults can carry otherwise insoluble drugs and protect them from degradation. Another modification is attaching a **cell-penetrating peptide (CPP)** like HIV's TAT peptide to the vault, which greatly improves the uptake of vaults by target cells [89]. These engineered vaults act like Trojan horses: stable in circulation, non-toxic, and capable of delivering a concentrated payload intracellularly. Studies have shown, for example, that TAT-modified vaults can enhance drug retention and penetration in tumor models [90] [89]. Vault nanoparticles have also been used to encapsulate entire virus particles (like adeno-associated virus vectors) by employing SpyTag/SpyCatcher technology, demonstrating the vault's capacity as a **molecular container** for gene therapy vectors [91]. Compared to synthetic nanoparticles, vaults have the benefit of being naturally monodisperse and less prone to clearance by the immune system or kidneys due to their size and human origin [86] [92]. All these features point to vaults as a promising platform for targeted drug delivery.

- **Vaccines and Immune Therapies:** Vault particles have been explored as novel vaccine carriers and immune modulators. Because vaults are normally "invisible" to the immune system when inside cells [93], they can be stealth delivery vehicles; but when engineered to carry antigens and released or administered, they can stimulate immune responses. Researchers have inserted immunogenic peptides or protein antigens into vaults (often by fusing them to either end of MVP or to the vault-associated INT domain, see below) and found that these vault-based vaccines can elicit robust antibody and T-cell responses. One advantage is that vaults can protect antigens from premature degradation and then naturally target them to antigen-presenting cells once outside cells [60]. Vaults have even been used to deliver cytokines in a localized manner: for instance, a vault carrying IL-15 (an immune stimulatory cytokine) has been tested as an immunotherapy approach, with the vault acting to concentrate IL-15 in tumors and reduce systemic toxicity. Vault Pharma, a biotechnology company co-founded by Leonard Rome, is advancing **vault-based immuno-oncology therapies** that leverage this approach [94] [95]. Their platform uses the vault's INT peptide (a fragment of VPARP that binds vault interiors with high affinity) to load vaults with cytokines or other immune-activating factors [96]. The idea is that vaults can deliver these signals directly to immune cells or the tumor microenvironment in a controlled fashion. Additionally, because vaults themselves may act as adjuvants when phagocytosed by dendritic cells (triggering danger signals as mentioned), a vault vaccine can potentially both present antigen and provide an innate immune kick-start.

- **Nanoreactors and Synthetic Biology:** The vault's interior cavity and customizable shell have also attracted interest in synthetic biology. By engineering pores or hinges in the vault shell, one can create vaults that open in response to certain stimuli (pH, light, or specific ligands), functioning as smart nanocontainers. Researchers have proposed using vaults as **nanoreactors** by packaging enzymes inside them. The vault shell could allow small substrates to diffuse in and out while retaining the enzyme, effectively compartmentalizing reactions at the nanoscale (similar to how virus-like particles are used to sequester enzymes). Another concept is attaching functional nanoparticles (like quantum dots or magnetic particles) to vaults for imaging or

targeting purposes – MVP's termini or the vault's exterior can be chemically conjugated without disrupting assembly [97] [98]. Efforts have even been made to organize vaults into higher-order structures or materials. Because vaults are naturally monodisperse and stable, they could serve as building blocks for nanofabrication. One study demonstrated a method for **covalently cross-linking vaults** into 2D lattices, potentially useful for creating novel biomaterials with regular 70 nm spacing (for filtration, scaffolding, etc.). In all these applications, the extensive engineering over the past decade has shown that vault particles are incredibly robust and **modular**. Vaults can be "decorated" with peptides, polymers, or targeting ligands to give them new properties [97] [99]. The large number of MVP subunits (78 per vault) means that a modification in the MVP sequence is effectively amplified 78-fold on the particle, allowing multivalent display of therapeutic molecules or targeting moieties. This multivalency can be exploited for high-avidity binding to cellular targets or for carrying a dense payload.

In practical terms, vault-based technologies are moving closer to clinical reality. Vault Pharma's pipeline includes an **"ImmunActiv"** vault that delivers immune stimulants as a cancer therapy, and an **"ImmunOncology"** vault that encapsulates tumor antigens to vaccinate patients' immune systems [100] [94]. Academic groups continue to publish new methods for vault modification, such as site-specific conjugation techniques that allow attaching drugs to vault surfaces with precise control [101]. The consensus in recent reviews is that vaults possess a unique combination of features making them ideal next-generation nanodevices: a large internal cavity for cargo, intrinsic stability in physiological conditions, avoidance of rapid clearance, and an ability to be taken up by cells efficiently when properly targeted [86] [92]. In the coming years, we may well see vault nanoparticles in clinical trials as drug carriers or vaccines – an impressive leap for an organelle whose function in the cell remains something of a mystery. In doing so, the engineering of vaults might even feedback to our basic understanding: by testing what vaults *can do* in a therapeutic context, we might gain clues about what they *do do* in their natural context.

Toward a Unifying Model for Vault Function

Drawing together the threads from structure, biology, and biotechnology, we can begin to sketch a unifying framework for what vault organelles might be doing in cells. Any satisfying model must account for several key facts: (1) vaults are *dispensable* under normal conditions, yet *highly conserved* and abundant – implying a role that is important but not constantly required; (2) vaults interact with diverse cellular pathways (transport, immune, signaling, etc.), suggesting a *multifunctional or conditional* role; (3) vaults have a large hollow structure with dynamic caps, hinting that *encapsulation and release* of cargo is central to their function; and (4) vault RNAs and associated proteins provide a direct link to gene regulation and stress responses, meaning vaults likely influence cellular decisions at a regulatory level.

One speculative model that aligns with these points is to envision vaults as **general-purpose cellular response modules** – organelles that remain inert most of the time, but can be rapidly deployed to handle various stressors or signaling events. In this view, vaults act as a kind of *"pre-packaged emergency kit"* for the cell. Under normal conditions, vaults might simply patrol the cytoplasm or sit near the nucleus, with their vault RNA content and any bound molecules safely tucked inside. When a certain threshold of stress is sensed (be it viral infection, exposure to toxins, DNA damage, or others), vaults could be activated to release or exchange their contents, or to relocate to a specific cellular site (like the nucleus or plasma membrane). The activation trigger might be chemical (e.g. a drop in pH causing the caps to open, as vaults are known to become unstable at pH 4–5 [102] [103]) or could be mediated by post-translational modifications (phosphorylation of MVP has been noted under some conditions [104]). Upon activation, vaults could perform tasks such as: dumping out small regulatory RNAs (svRNAs) to quickly alter gene expression programs; ferrying signaling proteins (like kinases or phosphatases) to new

locations to rewire pathways; or binding and sequestering harmful molecules (like reactive oxygen species or misfolded proteins) to mitigate damage. In a way, vaults would be like **cellular "vaults" for safekeeping** – they normally keep certain factors locked away, and when the vault "opens," those factors are unleashed to help the cell adapt.

This multi-faceted role could explain why vaults have been linked to seemingly disparate processes. For example, during an infection, vaults might open to release svRNAs that silence host genes and modulate immune responses (a double-edged sword that viruses could co-opt, as we see with vtRNA2-1 and PKR). During chemotherapy exposure, vaults might capture drug molecules or alter drug-metabolism gene expression via svRNAs, contributing to drug resistance. In development or differentiation, vaults might transport specific mRNAs or signaling proteins to particular subcellular regions, influencing cell fate decisions without being absolutely required for viability. The vault's structure – a large assembly with internally oriented binding sites (like the INT-binding sites for VPARP, or potential RNA-binding grooves) – supports the idea that vaults are built to carry a **diverse toolkit**. Interestingly, evolutionary analysis indicates that MVP (the structural core) appeared early, but other components (vRNA, VPARP, TEP1) were recruited later and possibly independently [17]. This could mean that the vault originally served a basic protective or transport function, and over time, cells added new "inserts" (like vRNAs) to tailor vaults to new roles (such as gene regulation). The result is a chimeric nanomachine that sits at the nexus of multiple cellular systems.

Another element of a unified theory is the concept of vaults as a **redundancy or buffering system**. Because vaults are not essential, cells might not rely on them for day-to-day functions, but vaults provide a backup or extra capacity when regular systems are overwhelmed. For instance, cells have dedicated transport proteins for nuclear-cytoplasmic trafficking (importins/exportins), dedicated drug efflux pumps, dedicated immune sensors, etc. Vaults might step in as an auxiliary system if those primary systems are stressed or if a rapid, transient response is needed. This would make vaults particularly useful in extreme conditions – which in evolutionary history might be episodic events like viral pandemics, drastic environmental changes, or periods of high metabolic stress. Species that faced these pressures might have been "saved" by their vaults, leading to strong conservation of vault genes. Species that didn't encounter such pressures (or evolved other mechanisms) lost their vaults without penalty. The distribution of vaults (present in vertebrates, many invertebrates, but absent in some parasites or organisms in stable niches) supports this idea that vaults are more crucial in complex, changing environments.

It is also possible that vaults do have a specific primary function that has simply been hard to identify because it is subtle or only occurs under certain conditions (for example, a role in neurodevelopment or aging). Some recent work points to MVP's involvement in processes like bone metabolism and osteoclast differentiation [105] and in modulating neuronal outgrowth via signaling pathways [104]. These could be downstream consequences of vaults' regulatory roles. A unifying framework might be that vaults ensure *homeostatic resilience* – they help cells return to equilibrium after perturbations by providing both storage of helpful molecules and removal of harmful ones. This "buffering" would manifest as mild phenotypes when vaults are knocked out (because cells only become significantly impaired in vault's absence when stressed).

Future Directions: Closing the Vault on the Vault Mystery

Solving the remaining mysteries of vault organelles will require creative approaches and new technologies. The next decade offers several exciting avenues to finally determine vaults' biological function:

- **Single-Cell and Spatial Proteomics:** Advanced proteomic techniques can identify vault-interacting proteins and cargo under various conditions with unprecedented sensitivity. By applying single-cell proteomics or imaging mass spectrometry, researchers could see if certain stresses cause new proteins to associate with vaults or if vault localization shifts within cells. For example, are vaults in immune cells carrying peptides or nucleic acids to the cell surface during antigen presentation? Do vaults in stressed cells bind to chaperones, metabolites, or damaged macromolecules? High-resolution spatial maps of vault components might reveal hotspots of vault activity (e.g. clustering at synapses in neurons, or at immune synapses in dendritic cells). Such data would highlight when and where vaults engage with specific cellular processes.

- **CRISPR Screens for Vault Function:** Genome-wide CRISPR knockout or activation screens can be deployed to find contexts in which vaults are crucial. One strategy is a **synthetic lethal screen**: knock out MVP (or vRNA genes) in a large pool of cells, then subject them to various challenges – viral infection, toxins, nutrient starvation, DNA damage, etc. – and see in which conditions MVP-knockout cells are selectively lost (indicating vaults were needed). Conversely, CRISPR activation screens could identify genes that when upregulated rescue any phenotype of vault loss, pointing to pathways vaults work in. If, say, vault-less cells die upon infection unless a certain cytokine pathway is boosted, that pathway could be where vaults normally act. Additionally, CRISPR could be used to make precise mutations in vault components (e.g. disrupt the PKR-binding motif in vRNA2-1 or the INT domain interaction) to test the importance of those interactions in vivo. These genetic screens across many conditions offer a powerful unbiased approach to catch vaults "in the act" of their function.

- **In Vivo Models and Stress Challenges:** Mouse models with vault component knockouts (MVP, TEP1, vPARP, and combinations thereof) have more to tell us, especially if we move beyond standard lab conditions. Future studies can involve exposing these mice to infections (viral, bacterial), carcinogens, metabolic stress (high-fat diet, etc.), or aging them to see if long-term differences emerge. It would be insightful to examine, for instance, whether MVP-knockout mice are more susceptible to viral encephalitis or have altered immune cell populations after a challenge, or whether aged vault-deficient mice show cognitive or regenerative defects that wild-type mice don't. Also, crossing vault-knockout mice with disease models (like cancer-prone or neurodegeneration-prone strains) might illuminate vaults' roles in those diseases. Given hints of vault involvement in immune signaling and drug resistance, these in vivo experiments under stress are likely to reveal phenotypes that justify vaults' evolutionary preservation.

- **Live-Cell Imaging and Vault Dynamics:** Technological advances in microscopy, such as single-molecule tracking and live-cell lattice light-sheet imaging, can capture vault behavior in real time. By tagging MVP or other vault components with fluorescent proteins (and ensuring vault assembly is not disturbed), researchers could watch vaults move within cells and even between cells. Do vaults traffic along microtubules? Do they transiently dock at the nuclear membrane or plasma membrane? Do they get secreted in exosomes or through unconventional secretion pathways? Live imaging during cell division might also be interesting – vaults redistribute evenly or are they strategically allocated to daughter cells? These dynamic studies, potentially combined

with **cryo-electron tomography** for ultra-structural context, will help correlate vault localization with function (e.g., vaults clustering at sites of active signal transduction or stress granules).

- **Comparative Genomics and Evolutionary Biology:** As more genomes across the tree of life are sequenced, we can better map where vault genes are present or absent and correlate that with species' ecology. For example, why did yeasts and plants lose vaults? Is there something about those lineages (perhaps cell wall presence, or a different antiviral strategy) that made vaults expendable? Conversely, organisms that retained vaults – do they share certain environmental pressures? A fascinating clue comes from the Atlantic salmon louse, a parasitic crustacean: it secretes MVP into an **extracellular cement** to stick eggs to its host [106]. This bizarre usage implies vault proteins can be co-opted for structural purposes in evolution. By examining unusual cases like this, or vault variants in diverse species, we might uncover hints of vaults' original role. Perhaps vaults were initially part of an ancient **virus-like particle** that eukaryotes domesticated – testing this might involve looking for remnants of vault-like elements in giant viruses or in bacteria. Evolutionary studies, including resurrecting ancestral MVP proteins and seeing what they do, could shed light on vaults' primordial function.

- **Biochemical Reconstitution and Cargo Identification:** On the biochemical front, isolating vaults from cells under different conditions and analyzing their contents with sensitive mass spectrometry or RNA sequencing is critical. For instance, do vaults from interferon-stimulated cells contain specific signaling factors not found in vaults from unstimulated cells? Modern proteomics could identify even transient vault interactors. Similarly, sequencing RNA from purified vault particles might detect transiently associated RNAs (beyond the known vRNAs) – perhaps vaults sometimes carry mRNAs or other small RNAs. Reconstituting vault function in vitro is another approach: can we load vaults with a particular protein or RNA and show delivery to nuclei or other compartments in cell-free systems? Such experiments would directly demonstrate transport capability. High-throughput approaches like proximity labeling (TurboID or APEX on vault components) might capture a snapshot of what's near vaults in situ, revealing microenvironments where vaults operate.

- **Integration with Other Cellular Systems:** Finally, a holistic understanding will require positioning vaults within the network of cellular pathways. Are vaults part of the innate immune sensing web (with NOD-like receptors, inflammasomes, etc.)? Do they interface with autophagy (perhaps being degraded or releasing contents via autophagosomes)? Do they contribute to intercellular communication (maybe vaults are secreted in exosomes or taken up by other cells)? Future research can explore these intersections. For example, one might examine if stress granules or P-bodies (RNA processing bodies) recruit vault components during stress, since vRNA might localize there. Or test if vaults are released during regulated cell death (like pyroptosis) as signals. Investigating these connections will clarify whether vaults are isolated oddities or integrated players in known cellular defense and communication pathways.

In conclusion, vault organelles stand as a compelling scientific enigma at the intersection of structure, cell biology, and evolution. Equipped with cutting-edge tools – from cryo-EM maps at atomic detail to single-cell omics – scientists are now poised to finally **unlock the secrets of the vault**. The vault's high conservation suggests it has a story to tell about eukaryotic cells' survival strategies across deep time. By pursuing the research directions outlined above, we have the opportunity to not only satisfy our curiosity about "the most enigmatic structure in cell biology" [81], but also to harness its potential for innovative medical technologies. The coming years will determine whether vaults remain a biological curiosity or emerge as a textbook-worthy example of cellular ingenuity. Either way, the vault is no longer forgotten – it has claimed its place in the spotlight, challenging us to open it and discover what treasures lie within.

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