**🔧 General Strategies to Increase Acceptance Likelihood**

**1. Sharpen the Core Hypothesis & Message**

**Problem**: The current proposal is technically sophisticated but thematically diffuse. Some reviewers struggled to identify what the central scientific question really is.

**Fix**:

* On the first page, clearly state a **testable, focused hypothesis**, e.g.:

“We hypothesize that enantiomeric specificity in terpene biosynthesis arises from conserved structural features in enzyme active sites that influence substrate folding and intermediate stabilization.”

* Emphasize the **biological significance**: Why does understanding enantiomerism matter for evolution, function, or application?

**2. Add a ‘Validation Plan’ Section — Even If Indirect**

**Problem**: Reviewers repeatedly noted the lack of **experimental validation**, which undermines the perceived impact.

**Fix**:

* Even without direct experiments, include a 3–4 line **“Validation Plan”** describing:
  + Planned collaborations.
  + Example predictions to test via mutagenesis and product analysis.
  + Intent to publish testable hypotheses that other labs can immediately act on.

This checks the “impact” and “realism” boxes without needing to overextend.

**3. Anticipate Reviewer Biases with Preemptive Clarifications**

Reviewers with differing backgrounds may:

* Misunderstand your use of ML (Reviewer 3)
* Be skeptical of rule generalization (Reviewer 4)
* Dismiss P450 and TPS being grouped together

**Fix**: Use **boxed clarification statements** or mini-subsections. For example:

* **Box: On the Use of Machine Learning**

“Where appropriate, we use ML to uncover structure-function trends in large datasets. Clustering and dimensionality reduction techniques are used alongside supervised models. We note that these are data analysis tools, not predictive black boxes.”

* **Box: TPS vs P450 Mechanistic Differences**

“While TPS and P450 enzymes catalyze fundamentally distinct chemistries (carbocation vs radical), this project tailors methods accordingly (RxnNet and QM/MM for TPS, different modules for P450s). The shared challenge is stereocontrol.”

**🔬 Scientific Suggestions to Strengthen the Proposal**

**1. Narrow Initial Focus on a Few Model Systems**

**Why**: Multiple reviewers noted the project is ambitious. Starting with a few well-characterized systems with known enantiomers makes it more tractable.

**How**:

* Explicitly define a **"core dataset"**: limonene, α-pinene, cineole, and one bacterial vs plant pair.
* Emphasize depth-first before scale:

“Initial work will focus on a tractable subset with known structures, enabling rigorous method validation before expanding to the broader enzyme space.”

**2. Explicitly Leverage Known Stereochemical Cases**

You mention limonene and cineole, but these aren’t tightly connected to your hypothesis in the original text.

**Fix**:

* Treat these examples as **case studies**:

“For example, our prior work shows O1/O2 preference in diphosphate binding correlates with enantiomeric product outcome in limonene synthases. We will expand on this to identify sequence/structure features that explain this stereodivergence.”

* Include 1–2 figures that show the mechanism + enantiomer outcome for these cases side by side.

**3. Be Realistic with AI Claims**

Reviewer 5 was unsure whether ML/AI is a strength or a liability.

**Fix**:

* Position AI as a **data augmentation and prioritization tool**, not a “magic bullet”:

“ML models will be used to identify promising enzyme candidates and reaction paths for deeper mechanistic simulation and docking. Interpretability and physical plausibility will guide all analysis.”

**4. Clarify Mechanistic Depth Over Broad Rule Mining**

**Why**: Reviewer 4 doubted that you could find generalizable rules.

**Fix**:

* Explicitly **shift from "rule discovery" to "mechanism-informed pattern recognition.”**
  + Say your goal is not to find universal rules but **common structural motifs, sequence signatures, or interaction patterns** that bias stereochemical outcomes.

**🛡️ How to Defend Against Unexpected Criticism**

**1. Create Reviewer Anchors**

Assume many reviewers skim. Use **clear section headers**, **highlight boxes**, and **summarized hypotheses** to anchor them. Some ideas:

* “Summary of Mechanistic Strategy for TPS vs P450”
* “Validation Approach”
* “Anticipated Outcome and Broader Impact”

**2. Bullet Point Your Strengths at the End of the Introduction**

Even in a science proposal, make your strengths impossible to miss:

* World-class expertise in TPS modeling
* Unique in-house tools (RxnNet, EnzyDock)
* Demonstrated feasibility via preliminary data
* High-impact problem in synthetic biology

**3. Tone & Confidence**

Avoid overly speculative language like “we aim to find…” or “we hope to uncover…”  
Use assertive, grounded phrasing:

“We will determine…”  
“We will apply our previously validated platform…”  
“We have the infrastructure and preliminary data to support…”

**✅ Final Touches That Help**

* **Visual flowchart** (like Figure 5) is great — enhance it slightly with clearer links between prediction and validation.
* **Limit jargon in key sections** — reviewers from adjacent fields may not know terms like "chirality fluidity" or "RxnNet reaction tree."
* **Use EnzyDock and RxnNet as "flagship tools"** — name them frequently so reviewers remember you're not starting from scratch.