**Figure S1.** Population coverage by the final set of epitopes.



**Figure S2.** Secondary structure of MEV optimized sequence mRNA

**Table S1.** MEV refined models prioritized based on the lowest galaxy energy. Structural statistics of the initial unrefined model is also given.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Model** | **RMSD** | **MolProbity** | **Clash score** | **Poor rotamers** | **Rama favored** | **GALAXY energy** |
| Initial | 0 | 3.522 | 145.6 | 2.4 | 87.7 | 12203.27 |
| MODEL 1 | 4.214 | 1.266 | 1.9 | 0 | 95.5 | -3151.35 |
| MODEL 2 | 4.372 | 1.523 | 3.4 | 0 | 94.2 | -3105.52 |
| MODEL 3 | 0.99 | 1.248 | 1.5 | 0 | 94.8 | -3096.46 |
| MODEL 4 | 3.931 | 1.356 | 3 | 0 | 96.1 | -3090.16 |
| MODEL 5 | 1.007 | 1.029 | 0.4 | 0 | 94.2 | -3080.71 |
| MODEL 6 | 3.478 | 1.448 | 3 | 0 | 94.8 | -3079.82 |
| MODEL 7 | 3.911 | 1.475 | 2.6 | 0 | 93.5 | -3071.57 |
| MODEL 8 | 3.556 | 1.361 | 2.3 | 0 | 94.8 | -3067.26 |
| MODEL 9 | 4.264 | 1.522 | 3.8 | 0 | 94.8 | -3062.72 |
| MODEL 10 | 3.945 | 1.407 | 2.6 | 0 | 94.8 | -3060.87 |

**Table S2.** TLR2 refined PatchDock complexes.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Rank** | **Solution Number** | **Global Energy** | **Attractive VdW** | **Repulsive VdW** | **ACE** | **HB** |
|  |  | ↓ |  |  |  |  |
| 1 | 5 | -14.33   | -42.75     | 32.11      | 7.58   | -5.46   |
| 2 | 8 | -4.04   | -3.91     | 0.82      | 2.10   | -2.24   |
| 3 | 3 | 2.66   | -24.16     | 11.24      | 10.72   | -1.19   |
| 4 | 7 | 12.10   | -13.47     | 5.18      | 3.53   | -1.93   |
| 5 | 2 | 29.00   | -1.54     | 0.00      | 2.89   | 0.00   |
| 6 | 1 | 38.81   | -9.70     | 3.68      | 8.76   | -1.25   |
| 7 | 9 | 67.52   | -30.98     | 36.81      | 15.76   | -3.34   |
| 8 | 6 | 70.90   | -15.52     | 92.10      | 7.00   | -1.08   |
| 9 | 4 | 195.27   | -18.64     | 213.18      | 15.43   | -0.79   |
| 10 | 10 | 3930.96   | -41.19     | 4906.37      | 5.16   | -6.42   |

\*VdW (van der Waals), ACE (Atomic Contact Energy), HB (Hydrogen Bonding).

**Table S3.** TLR3 refined PatchDock complexes.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Rank** | **Solution Number** | **Global Energy** | **Attractive VdW** | **Repulsive VdW** | **ACE** | **HB** |
|  |  | ↓ |  |  |  |  |
| 1 | 9 | -6.95   | -7.70     | 1.50      | -2.47   | 0.00   |
| 2 | 7 | -4.70   | -26.88     | 4.98      | 10.51   | -2.81   |
| 3 | 4 | -3.59   | -38.77     | 16.29      | 14.37   | -1.89   |
| 4 | 8 | -3.13   | -8.60     | 4.06      | 2.02   | -2.74   |
| 5 | 3 | 5.60   | -2.68     | 0.79      | 2.12   | 0.00   |
| 6 | 6 | 13.68   | -26.63     | 28.19      | 13.63   | -4.19   |
| 7 | 2 | 22.90   | -13.65     | 18.59      | 9.08   | -2.32   |
| 8 | 10 | 29.81   | -23.23     | 12.66      | 2.17   | -1.56   |
| 9 | 5 | 34.06   | -5.68     | 9.45      | 6.89   | -0.35   |
| 10 | 1 | 43.55   | -13.42     | 1.99      | 9.81   | -3.96   |

\*VdW (van der Waals), ACE (Atomic Contact Energy), HB (Hydrogen Bonding).

**Table S4**. List of hotspot residues in MMGBSA and MMPBSA

|  |
| --- |
| **MEV-TLR2** |
|  **MMGBSA** |  **MMPBSA** |
| Total Energy | Sidechain Energy | Backbone Energy | Total Energy | Sidechain Energy | Backbone Energy |
| Ser33 | -5.4 | Ser33 | -4.4 | Ser33 | -1.0 | Ser33 | -6.7 | Ser33 | -5.7 | Ser33 | -1.0 |
| Ser56 | -6.7 | Ser56 | -5.7 | Ser56 | -1.0 | Ser56 | -7.1 | Ser56 | -7.0 | Ser56 | -0.1 |
| Lys55 | -2.7 | Lys55 | -2.0 | Lys55 | -0.7 | Lys55 | -4.8 | Lys55 | -3.8 | Lys55 | -1.0 |
| Gln79 | -7.1 | Gln79 | -5.8 | Gln79 | -1.3 | Gln79 | -3.8 | Gln79 | -3.5 | Gln79 | -0.3 |
| Gln152 | -3.4 | Gln152 | -2.9 | Gln152 | -0.5 | Gln152 | -1.9 | Gln152 | -1.5 | Gln152 | -0.4 |
| Asn177 | -8.4 | Asn177 | -7.4 | Asn177 | -1.0 | Asn177 | -7.5 | Asn177 | -7.0 | Asn177 | -0.5 |
| Val80 | -2.4 | Val80 | -2.2 | Val80 | -0.2 | Val80 | -8.4 | Val80 | -7.4 | Val80 | -1.0 |
| Gly344 | -9.4 | Gly344 | -8.7 | Gly344 | -0.7 | Gly344 | -5.9 | Gly344 | -3.9 | Gly344 | -2.0 |
| Asn345 | -1.4 | Asn345 | -1.2 | Asn345 | -0.2 | Asn345 | -4.8 | Asn345 | -3.8 | Asn345 | -1.0 |
| Arg422 | -1.9 | Arg422 | -1.7 | Arg422 | -0.7 | Arg422 | -3.8 | Arg422 | -3.2 | Arg422 | -0.6 |
| Tyr483 | -4.7 | Tyr483 | -4.0 | Tyr483 | -0.7 | Tyr483 | -6.4 | Tyr483 | -5.4 | Tyr483 | -1.0 |
| Val503 | -4.1 | Val503 | -3.1 | Val503 | -1.1 | Val503 | -5.7 | Val503 | -5.0 | Val503 | -0.7 |
| Lys505 | -4.8 | Lys505 | -3.7 | Lys505 | -1.1 | Arg422 | -5.9 | Arg422 | -4.9 | Arg422 | -1.0 |
| Arg507 | -6.1 | Arg507 | -6.0 | Arg507 | -6.0 |  |  |  |  |  |  |
| Val556 | -5.7 | Val556 | -5.1 | Val556 | -0.6 |  |  |  |  |  |  |
| Asp557 | -2.7 | Asp557 | -2.0 | Asp557 | -0.7 |  |  |  |  |  |  |
| Glu629 | -1.8 | Glu629 | -1.3 | Glu629 | -0.5 |  |  |  |  |  |  |
| **MEV-TLR3** |
|  **MMGBSA** |  **MMPBSA** |
| Total Energy | Sidechain Energy | Backbone Energy | Total Energy | Sidechain Energy | Backbone Energy |
| Hie3 | -2.85 | Val1 | -1.84 | Hie3 | -1.61 | Arg454 | -8.09 | Val1 | -1.79 | Hie3 | -1.43 |
| Val5 | -1.15 | Hie3 | -1.24 | Thr137 | 0.00 | Arg453 | -7.83 | Asp7 | -1.88 | Leu175 | 0.00 |
| Asp7 | -2.49 | Val5 | -1.14 | Cys187 | 0.00 | Arg704 | -6.13 | Arg453 | -7.35 | Glu628 | -1.61 |
| Leu135 | 0.00 | Asp7 | -2.25 | Hie189 | 0.00 | Arg646 | -6.05 | Arg454 | -7.80 | Thr629 | -2.26 |
| Asn143 | 0.00 | Lys60 | 0.00 | Asn218 | 0.00 | Glu722 | -5.65 | Phe609 | -1.04 |   |   |
| Ala190 | 0.00 | Val115 | 0.00 | Trp244 | 0.00 | Lys637 | -4.09 | Phe622 | -2.73 |   |   |
| Ser207 | 0.00 | Val139 | 0.00 | Thr248 | 0.00 | Lys679 | -3.57 | Asn627 | -1.05 |   |   |
| Asn236 | 0.00 | Ser159 | 0.00 | Ser315 | 0.00 | Thr629 | -3.21 | Lys637 | -3.74 |   |   |
| Thr237 | 0.00 | Ser207 | 0.00 | Ser368 | 0.00 | Tyr638 | -3.14 | Tyr638 | -2.37 |   |   |
| Leu242 | 0.00 | Leu247 | 0.00 | Asp390 | 0.00 | Lys720 | -3.01 | Val642 | -1.31 |   |   |
| Met249 | 0.00 | Trp267 | 0.00 | Ala514 | 0.00 | Phe622 | -2.78 | Arg646 | -6.44 |   |   |
| Ala266 | 0.00 | Ser286 | 0.00 | Glu628 | -1.01 | Asp7 | -2.26 | Val649 | -1.19 |   |   |
| Gly291 | 0.00 | Cys321 | 0.00 | Cys686 | -1.44 | Hie3 | -2.08 | Lys679 | -3.38 |   |   |
| Ser337 | 0.00 | Leu343 | 0.00 |   |   | Val743 | -1.71 | Trp688 | -1.35 |   |   |
| Leu343 | 0.00 | Ser372 | 0.00 |   |   | Phe721 | -1.52 | Arg704 | -5.87 |   |   |
| Asp390 | 0.00 | Leu374 | 0.00 |   |   | Val642 | -1.45 | Lys720 | -3.29 |   |   |
| Arg453 | -5.83 | Gly414 | 0.00 |   |   | Trp688 | -1.39 | Phe721 | -1.67 |   |   |
| Arg454 | -5.91 | Gly419 | 0.00 |   |   | Val649 | -1.39 | Glu722 | -5.53 |   |   |
| Ser463 | 0.00 | Ala442 | 0.00 |   |   | Thr744 | -1.33 | Val743 | -1.37 |   |   |
| Thr603 | -2.01 | Arg453 | -5.71 |   |   | Hie683 | -1.23 | Thr744 | -1.13 |   |   |
| Phe609 | -1.15 | Arg454 | -6.04 |   |   | Cys686 | -1.11 |   |   |   |   |
| Ile619 | -1.06 | Pro543 | 0.00 |   |   | Gln694 | -1.11 |   |   |   |   |
| Phe622 | -3.47 | Thr603 | -2.13 |   |   | Arg692 | -1.10 |   |   |   |   |
| Asn627 | -1.04 | Phe609 | -1.21 |   |   | Val5 | -1.07 |   |   |   |   |
| Glu628 | -1.03 | Ile619 | -1.25 |   |   | Phe609 | -1.06 |   |   |   |   |
| Thr629 | -1.31 | Phe622 | -3.57 |   |   | Gly136 | 0.00 |   |   |   |   |
| Thr634 | -2.18 | Asn627 | -1.33 |   |   | Ile387 | 0.00 |   |   |   |   |
| Lys637 | -2.06 | Thr634 | -1.89 |   |   |   |   |   |   |   |   |
| Tyr638 | -3.80 | Lys637 | -2.53 |   |   |   |   |   |   |   |   |
| Arg641 | -1.92 | Tyr638 | -3.35 |   |   |   |   |   |   |   |   |
| Val642 | -1.72 | Arg641 | -2.12 |   |   |   |   |   |   |   |   |
| Arg646 | -5.03 | Val642 | -1.55 |   |   |   |   |   |   |   |   |
| Val649 | -1.50 | Arg646 | -5.63 |   |   |   |   |   |   |   |   |
| Lys679 | -2.72 | Val649 | -1.38 |   |   |   |   |   |   |   |   |
| Hie683 | -1.40 | Lys679 | -2.83 |   |   |   |   |   |   |   |   |
| Cys686 | -2.32 | Hie683 | -1.35 |   |   |   |   |   |   |   |   |
| Trp688 | -2.95 | Trp688 | -2.96 |   |   |   |   |   |   |   |   |
| Gln694 | -1.67 | Gln694 | -1.53 |   |   |   |   |   |   |   |   |
| Arg704 | -5.84 | Arg704 | -6.02 |   |   |   |   |   |   |   |   |
| Lys720 | -1.06 | Lys720 | -2.36 |   |   |   |   |   |   |   |   |
| Phe721 | -1.24 | Phe721 | -1.37 |   |   |   |   |   |   |   |   |
| Glu722 | -6.29 | Glu722 | -6.22 |   |   |   |   |   |   |   |   |
| Val743 | -2.01 | Val743 | -1.62 |   |   |   |   |   |   |   |   |
| Thr744 | -1.11 | Thr744 | -1.15 |   |   |   |   |   |   |   |   |