BRIEF SUMMARY

[0008a] In an aspect of the present disclosure, there is provided a use of a SOS1 inhibitor in the manufacture of a medicament for treating a subject having a disease or disorder associated with cells having a SHP2 mutation.

[0009] In some ~~aspect~~examples, the present disclosure is directed to a method of treating a subject having a disease or disorder associated with cells having a SHP2 mutation. The method comprises administering to the subject a therapeutically effective amount of a SOS1 inhibitor alone or in combination with an additional therapeutic agent.

[0010] In some ~~aspect~~examples, the SHP2 mutation induces an activated form of SHP2.

[0011] In some ~~aspect~~examples, the subject expressed the SHP2 mutation after prior treatment with a SHP2 inhibitor. In some ~~aspect~~examples, the subject expressed the SHP2 mutation after prior treatment with an allosteric SHP2 inhibitor.

[0012] In some ~~aspect~~examples, the method further comprises administering to the subject a therapeutically effective amount of a RAS inhibitor selected from the group consisting of a RAS(ON) inhibitor, a RAS(OFF) inhibitor, and a combination thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] FIG. 1 is an illustration of the RAS-MAPK pathway. SHP2 activates SOS1, which, in turn, activates RAS, leading to signaling that drives cell growth and survival.

[0014] FIG. 2A is a graph depicting activating mutations in SHP2, which reduce sensitivity to inhibition with a SHP2 allosteric inhibitor, RMC-4550. As shown in the graph, cellular sensitivity correlates with energetic magnitude (ΔG_{op}) of SHP2 activating mutations. Lower ΔG_{op} indicates stronger activation. FIG. 2B is a table showing the IC_{50} concentrations of RMC-4550 sufficient to inhibit SHP2 proteins with activating mutations. As shown in the table, strongly activating mutations, such as G503V, require high concentrations of allosteric SHP2 inhibitor to achieve a response. These data were obtained according to the methods disclosed in Example 1.

[0015] FIGS. 3A and 3B are graphs showing that SOS1 inhibitors maintain sensitivity in isogenic HEK-293 cell lines carrying a SHP2 E76K mutant. These data were obtained according to the methods disclosed in Example 1.

[0016] FIGS. 4A through 4H are graphs showing that activating mutations induce resistance to allosteric SHP2 inhibition but maintain sensitivity to SOS1 inhibitors in

We Claim:

1. Use of a SOS1 inhibitor in the manufacture of a medicament for ~~A method of~~ treating a subject having a disease or disorder associated with cells having a SHP2 mutation~~, the method comprising:~~

~~administering to the subject a therapeutically effective amount of a SOS1 inhibitor~~.

2. The ~~method~~use of claim 1, wherein the SHP2 mutation induces an activated form of SHP2.

3. The ~~method~~use of claim 1, wherein the subject expressed the SHP2 mutation after prior treatment with a SHP2 inhibitor.

4. The ~~method~~use of claim 1, wherein the subject expressed the SHP2 mutation after prior treatment with an allosteric SHP2 inhibitor.

5. The ~~method~~use of claim 3 or claim 4, wherein the SHP2 inhibitor or a pharmaceutically acceptable salt, solvate, stereoisomer, prodrug, or tautomer thereof is selected from those disclosed in WO 2021149817, WO 2021148010, WO 2021147879, WO 2021143823, WO 2021143701, WO 2021143680, WO2021121397, WO 2021119525, WO 2021115286, WO 2021110796, WO 2021088945, WO 2021073439, WO 2021061706, WO 2021061515, WO 2021043077, WO 2021033153, WO 2021028362, WO 2021033153, WO 2021028362, WO 2021018287, WO 2020259679, WO 2020249079, WO 2020210384, WO 2020201991, WO 2020181283, WO 2020177653, WO 2020165734, WO 2020165733, WO 2020165732, WO 2020156243, WO 2020156242, WO 2020108590, WO 2020104635, WO 2020094104, WO 2020094018, WO 2020081848, WO 2020073949, WO 2020073945, WO 2020072656, WO 2020065453, WO 2020065452, WO 2020063760, WO 2020061103, WO 2020061101, WO 2020033828, WO 2020033286, WO 2020022323, WO 2019233810, WO 2019213318, WO 2019183367, WO 2019183364, WO 2019182960, WO 2019167000, WO 2019165073, WO 2019158019, WO 2019152454, WO 2019051469, WO 2019051084, WO 2018218133, WO 2018172984, WO 2018160731, WO 2018136265, WO 2018136264, WO 2018130928, WO 2018129402, WO 2018081091, WO 2018057884, WO 2018013597, WO 2017216706, WO 2017211303, WO 2017210134, WO 2017156397, WO 2017100279, WO 2017079723, WO 2017078499, WO

2016203406, WO 2016203405, WO 2016203404, WO 2016196591, WO 2016191328, WO 2015107495, WO 2015107494, WO 2015107493, WO 2014176488, WO 2014113584, US 20210085677, US 10858359, US 10934302 and US 10954243.

6. The ~~method~~use of claim 3 or claim 4, wherein the SHP2 inhibitor or a pharmaceutically acceptable salt, solvate, stereoisomer, prodrug, or tautomer thereof is selected from the group consisting of ERAS-601, BBP-398, RLY-1971, JAB-3068, JAB-3312, TNO155, SHP099, RMC-4550, and RMC-4630.

7. The ~~method~~use of claim 3 or 4, wherein the SHP2 inhibitor is TNO155 or RMC-4630, or a pharmaceutically acceptable salt, solvate, stereoisomer, prodrug, or tautomer thereof.

8. The ~~method~~use of claim 7, wherein the SHP2 inhibitor is RMC-4630, or a pharmaceutically acceptable salt, solvate, stereoisomer, prodrug, or tautomer thereof.

9. The ~~method~~use of claim 1, wherein the SHP2 mutation confers resistance to a SHP2 inhibitor or an allosteric SHP2 inhibitor.

10. The ~~method~~use of any one of claims 1 through 9, wherein SHP2 mutation is at a position selected from the group consisting of T52, I56, G60, D61, Y62, Y63, E69, K70, A72, T73, E76, E123, E139, Y197, S189, T253, Q257, L261, L262, R265, F285, N308, V428, A461, T468, P491, S502, G503, M504, Q506, Q510, T507, and a combination thereof.

11. The ~~method~~use of any one of claims 1 through 10, wherein the SHP2 mutation is at a position selected from the group consisting of A72, E76 and G503, and a combination thereof.

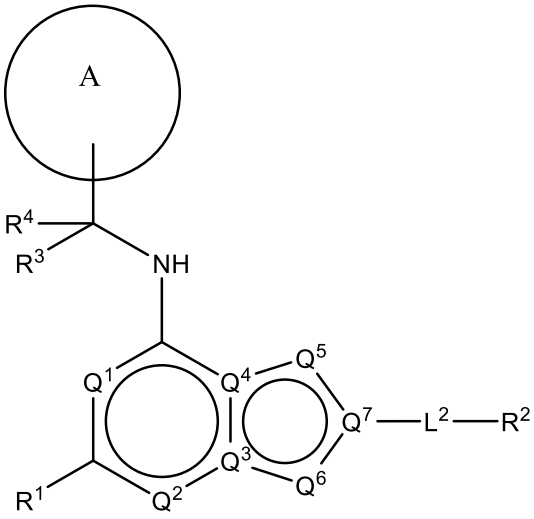
12. The ~~method~~use of any one of claims 1 through 9, wherein SHP2 mutation is selected from the group consisting of T52I, I56V, G60V, D61G, D61V, D61Y, Y62D, Y63D, Y63C, E69K, E69Q, K70R, A72S, A72T, A72V, T73I, E76A, E76G, E76K, E76Q, E123D, E139D, S189A, T253M, Q257L, L261F, L261H, L262R, R265Q, F285S, N308D, V428M, A461T, A461G, T468M, P491S, S502L, S502P, G503A, G503V, M504V, Q506P, T507K, Q510P, Q510H, and a combination thereof.

13. The ~~method~~use of any one of claims 1 through 12, wherein SHP2 mutation is selected from the group consisting of G60V, D61G, D61V, E69K, A72S, A72T, A72V, T73I, E76A, E76G, E76K, E76Q, S189A, L262R, F285S, N308D, T468M, P491S, S502P, G503V, Q506P, T507K, T253M/Q257L, and a combination thereof.

14. The ~~method~~use of any one of claims 1 through 13, wherein SHP2 mutation is selected from the group consisting of A72V, E76K, or G503V, and a combination thereof.

15. The ~~method~~use of any one of claims 1 through 14, wherein the SOS1 inhibitor or a pharmaceutically acceptable salt, solvate, stereoisomer, prodrug, or tautomer thereof is selected from those disclosed in WO 2018/115380, WO 2018/172250, WO 2019/122129, and WO 2019/201848.

16. The ~~method~~use of any one of claims 1 through 14, wherein the SOS1 inhibitor is a compound having the structure of Formula (41-I),



(41-I)

or a pharmaceutically acceptable salt, solvate, stereoisomer, prodrug, or tautomer thereof, wherein:

Q^1 and Q^2 are independently CH or N;

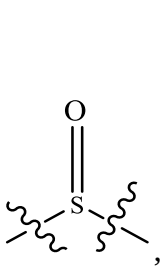
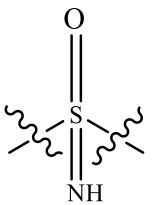
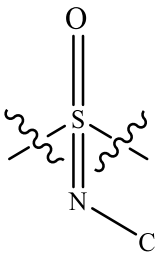
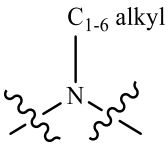
Q^3, Q^4, and Q^7 are independently C or N, wherein at least one of Q^3 and Q^4 is C and wherein Q^3, Q^4, and Q^7 are not all N;

Q^5 is CH, N, NH, O, or S;

Q^6 is CH, N, NH, N-C_{1-6} alkyl, N-C_{1-6} heteroalkyl, N-(3-7 membered cycloalkyl), N-(3-7 membered heterocyclyl), O, or S;

wherein at least one of Q^1, Q^2, Q^3, Q^4, Q^5, Q^6, and Q^7 is N, NH, O, or S;

R^1 is selected from the group consisting of H, C_{1-6} alkyl, halogen, -NHR^{1a}, –OR^{1a}, cyclopropyl, and –CN; wherein C_{1-6} alkyl is optionally substituted with halogen, -NHR^{1a}, or –OR^{1a}; wherein R^{1a} is H, C_{1-6} alkyl, 3-6 membered heterocyclyl, or C_{1-6} haloalkyl;

L^2 is selected from the group consisting of a bond, –C(O)–, –C(O)O–, –C(O)$NH(CH_2)_o$–, –$S(O)_2$–, , , , , –C(O)$(CH_2)_p$–, –$(CH_2)_p$–, and –O–; wherein o is 0, 1, or 2; and wherein p is a number from 1 to 6;

R^2 is selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, -$NR^{2b}R^{2c}$, -OR^{2a}, 3-14 membered cycloalkyl, 3-14 membered cycloalkenyl, 3-14 membered heterocyclyl, 6-10 membered aryl, and 5-10 membered heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, 3-14 membered cycloalkyl, 3-14 membered cycloalkenyl, 3-14 membered heterocyclyl, 6-10 membered aryl, and 5-10 membered heteroaryl are independently optionally substituted with C_{1-6} alkyl, C_{1-6} haloalkyl, –OH, -OR^{2a}, oxo, halogen, –C(O)R^{2a}, –C(O)OR^{2a}, –C(O)$NR^{2b}R^{2c}$, –CN, -$NR^{2b}R^{2c}$, 3-6 membered cycloalkyl, 3-7 membered heterocyclyl, 6-10 membered aryl, or 5-10 membered heteroaryl;

wherein R^{2a} is H, C_{1-6} alkyl, C_{1-6} haloalkyl, 3-7 membered heterocyclyl, or –$(CH_2)_rOCH_3$, wherein r is 1, 2, or 3;

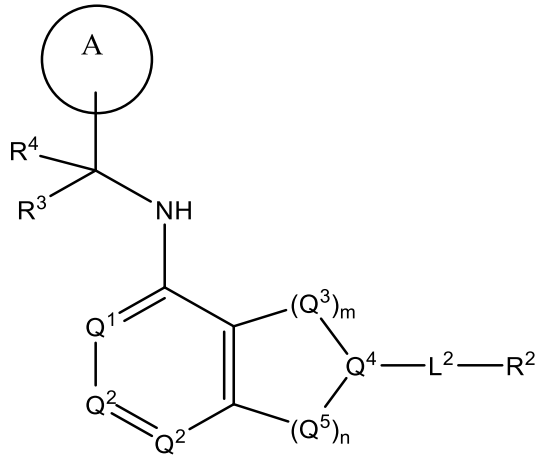
wherein R^{2b} is H or C_{1-6} alkyl;

wherein R^{2c} is H or C_{1-6} alkyl;

R^3 and R^4 are independently H or C_{1-6} alkyl optionally substituted with halo or -OH; wherein at least one of R^3 and R^4 is H or wherein R^3 and R^4 together with the atom to which they are attached combine to form a 3-6 membered cycloalkyl; and

A is an optionally substituted 6-membered aryl or an optionally substituted 5-6 membered heteroaryl.

17. The ~~method~~use of any one of claims 1 through 14, wherein the SOS1 inhibitor is a compound having the structure of Formula (42-I),



(42-I)

or a pharmaceutically acceptable salt, solvate, stereoisomer, prodrug, or tautomer thereof, wherein:

Q^1 is CH or N;

Q^4 is CH, C, or N;

each Q^2 is independently C-R^1 or N, wherein one Q^2 is N and the other Q^2 is C-R^1;

each Q^3 and Q^5 are independently $C(R^{QC})_2$, NR^{QN}, CO, O, S, or SO_2, wherein each R^{QC} is independently H, F, Cl, Br, or 6-10 membered aryl, and wherein each R^{QN} is independently H, C_{1-6} alkyl, or 6-10 membered aryl;

wherein at least one of Q^1, Q^2, Q^3, Q^4, and Q^5 is N, NR^{QN}, O, or SO_2;

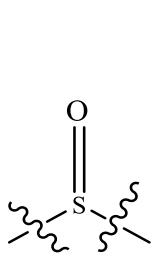
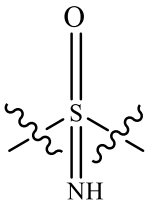
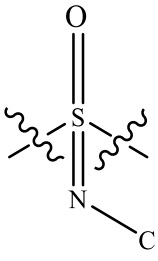
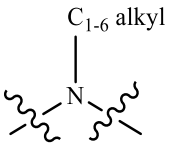
m is 0, 1, 2, or 3;

n is 0, 1, 2, or 3;

wherein when m is 0, then n is not 0;

R^1 is selected from the group consisting of H, C_{1-6} alkyl, halogen, -$CONHR^{1a}$, -NHR^{1a}, –OR^{1a}, cyclopropyl, azetidinyl, and –CN; wherein each C_{1-6} alkyl and azetidinyl is

optionally substituted with halogen, R^{1a}, -NHR^{1a}, or –OR^{1a}; wherein R^{1a} is H, C_{1-6} alkyl, cyclopropyl, 3-6 membered heterocyclyl, or C_{1-6} haloalkyl;

L^2 is selected from the group consisting of a bond, –C(O)–, –C(O)O–, –C(O)$NH(CH_2)_o$–, –$S(O)_2$–, , , , , –$C(O)(CH_2)_p$–, –$(CH_2)_p$–, and –O–; wherein o is 0, 1, or 2; and wherein p is a number from 1 to 6;

R^2 is selected from the group consisting of H, C_{1-6} alkyl, -$NR^{2b}R^{2c}$, -OR^{2a}, 3-14 membered cycloalkyl, 3-14 membered cycloalkenyl, 3-14 membered heterocyclyl, 6-10 membered aryl, and 5-10 membered heteroaryl; wherein each C_{1-6} alkyl, 3-14 membered cycloalkyl, 3-14 membered cycloalkenyl, 3-14 membered heterocyclyl, 6-10 membered aryl, and 5-10 membered heteroaryl are independently optionally substituted with C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} methoxyalkyl, –OH, –OR^{2a}, oxo, =N, halogen, –$C(O)R^{2a}$, –$C(O)OR^{2a}$, –$C(O)NR^{2b}R^{2c}$, -SO_2R^{2a}, –CN, -$NR^{2b}R^{2c}$, 3-6 membered cycloalkyl, 3-7 membered heterocyclyl, 6-10 membered aryl, or 5-10 membered heteroaryl;

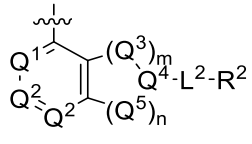
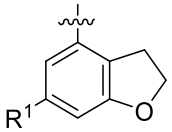
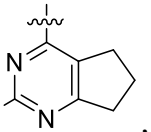
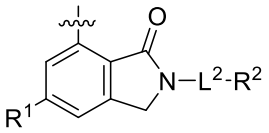
wherein R^{2a} is H, C_{1-6} alkyl, C_{1-6} haloalkyl, 3-7 membered heterocyclyl, or –$(CH_2)_rOCH_3$, wherein r is 1, 2, or 3;

wherein R^{2b} is H or C_{1-6} alkyl;

wherein R^{2c} is H or C_{1-6} alkyl;

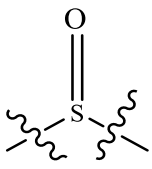
R^3 and R^4 are independently H or C_{1-6} alkyl optionally substituted with halo or -OH; wherein at least one of R^3 and R^4 is H or wherein R^3 and R^4 together with the atom to which they are attached combine to form a 3-6 membered cycloalkyl; and

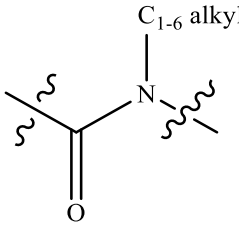
A is an optionally substituted 6-membered aryl or an optionally substituted 5-6 membered heteroaryl;

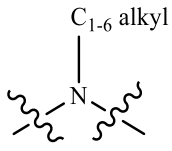
with the proviso that when  is , , ,

R_2 is selected from the group consisting of H, C_{1-6} alkyl, halogen, -NHR_{2a}, –OR_{2a}, cyclopropyl, and –CN; wherein C_{1-6} alkyl is optionally substituted with halogen, -NHR_{2a}, –OR_{2a}, or 5-6 membered heterocyclyl, and further wherein R_{2a} is selected from the group consisting of H, C_{1-6} alkyl, 3-6 membered heterocyclyl, and C_{1-6} haloalkyl;

R_3 is selected from the group consisting of H, C_{1-3} alkyl, –OR_{3a}, cyclopropyl, and 3-6 membered heterocyclyl, wherein each of C_{1-3} alkyl, cyclopropyl, and 3-6 membered heterocyclyl is optionally substituted with R_{3a}, and further wherein R_{3a} is selected from the group consisting of C_{1-3} alkyl, halogen, –OH, and –CN;

L_4 is selected from the group consisting of bond, –C(O)–, –C(O)O–, –C(O)$NH(CH_2)_o$–, –NH–, –S–, –$S(O)_2$–, 

, 

, 

, –$(CH_2)_p$–, and –O–; wherein o is 0, 1, or 2; and wherein p is a number from 1 to 6; and

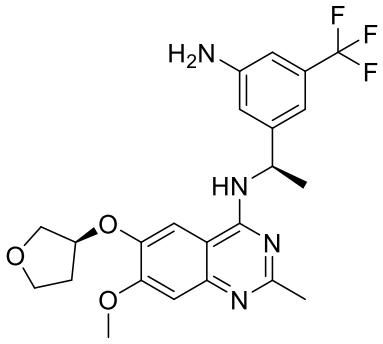
R_4 is selected from the group consisting of H, C_{1-6} alkyl, 3-14 membered cycloalkyl, 3-14 membered cycloalkenyl, 3-14 membered heterocyclyl, 6-10 membered aryl, and 5-10 membered heteroaryl; wherein each C_{1-6} alkyl, 3-14 membered cycloalkyl, 3-14 membered cycloalkenyl, 3-14 membered heterocyclyl, 6-10 membered aryl, and 5-10 membered heteroaryl is optionally substituted with C_{1-6} alkyl, –R_{4a}, –OR_{4a}, –O–C_{1-6} alkyl–R_{4a}, =O, halogen, –C(O)R_{4a}, –C(OO)R_{4a}, –C(O)$NR_{4b}R_{4c}$, –NR_{4b}C(O)R_{4c}, –CN, =NR_{4a}, –$NR_{4b}R_{4c}$, –SO_2R_{4a}, 3-6 membered cycloalkyl, 3-7 membered heterocyclyl, 6-10 membered aryl, or 5-10 membered heteroaryl;

wherein R_{4a} is H, C_{1-6} alkyl, C_{1-6} haloalkyl, –C(O)$NR_{4b}R_{4c}$, 3-6 membered cycloalkyl, 6-10 membered aryl optionally substituted with –OR_{4b}, –CN, 3-7 membered heterocyclyl, –$(CH_2)_rOCH_3$, or –$(CH_2)_rOH$, wherein r is 1, 2, or 3;

wherein each R_{4b} is independently H, C_{1-6} alkyl; and

wherein each R_{4c} is independently H or C_{1-6} alkyl.

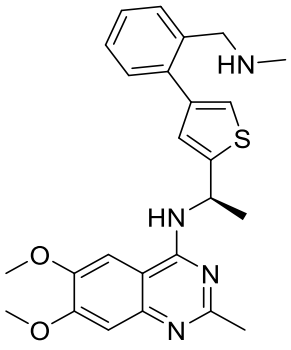
19. The ~~method~~use of any one of claims 1 through 14, wherein the SOS1 inhibitor is BI-3406, having the structure:



or a pharmaceutically acceptable salt, solvate, stereoisomer, prodrug, or tautomer thereof.

20. The ~~method~~use of any one of claims 1 through 14, wherein the SOS1 inhibitor is BI-1701963 or a pharmaceutically acceptable salt, solvate, stereoisomer, prodrug, or tautomer thereof.

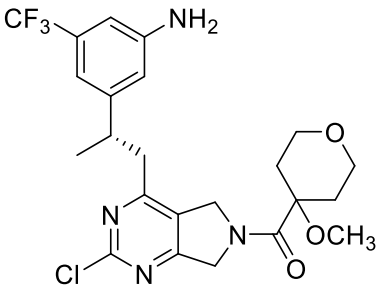
21. The ~~method~~use of any one of claims 1 through 9, wherein the SOS1 inhibitor is BAY-293, having the structure:



or a pharmaceutically acceptable salt, solvate, stereoisomer, prodrug, or tautomer thereof.

22. The ~~method~~use of any one of claims 1 through 14, wherein the SOS1 inhibitor is SDGR5 or a pharmaceutically acceptable salt, solvate, stereoisomer, prodrug, or tautomer thereof.

23. The ~~method~~use of any one of claims 1 through 14, wherein the SOS1 inhibitor is Compound SOS1-(A) (also called RMC-0331), having the structure:



or a pharmaceutically acceptable salt, solvate, stereoisomer, prodrug, or tautomer thereof.

24. The ~~method~~use of any one of claims 1 through 14, wherein the SOS1 inhibitor is Compound SOS1-(B) or a pharmaceutically acceptable salt, solvate, stereoisomer, prodrug, or tautomer thereof.

25. The ~~method~~use of any one of claims 1 through 24, ~~further comprising administering~~ wherein the SOS1 inhibitor is to be administered to the subject, and wherein ~~a therapeutically effective amount of~~ a RAS inhibitor is to be further administered to the subject.

26. The ~~method~~use of claim 25, wherein the RAS inhibitor is selected from the group consisting of a RAS(ON) inhibitor, a RAS(OFF) inhibitor, MRTX1133 or a pharmaceutically acceptable salt, solvate, stereoisomer, prodrug, or tautomer thereof, and a combination thereof.

27. The ~~method~~use of claim 25, wherein the RAS inhibitor is selective for a mutation at position 12 or 13 of a RAS protein.

28. The ~~method~~use of any one of claims 25 through 27, wherein the RAS inhibitor is a RAS(ON) inhibitor.

29. The ~~method~~use of claim 28, wherein the RAS(ON) inhibitor is an inhibitor selective for RAS G12C, RAS G13D, or RAS G12D.

30. The ~~method~~use of claim 28, wherein the RAS(ON) inhibitor is a $RAS(ON)^{MULTI}$ inhibitor.

31. The ~~method~~use of claim 28, wherein the RAS(ON) inhibitor is selected from a compound of any one of Appendices A, B, C, or D, or a compound described by a Formula of any one of Appendices A, B, C, or D, or a pharmaceutically acceptable salt, solvate, stereoisomer, prodrug, or tautomer thereof.

32. The ~~method~~use of claim 31, wherein the RAS(ON) inhibitor is a compound described by Formula I in Appendix A, or a pharmaceutically acceptable salt, solvate, stereoisomer, prodrug, or tautomer thereof.

33. The ~~method~~use of claim 32, wherein the RAS(ON) inhibitor is selected from a compound of Table 1 or Table 2 of Appendix A, or a pharmaceutically acceptable salt, solvate, stereoisomer, prodrug, or tautomer thereof.

34. The ~~method~~use of claim 31, wherein the RAS(ON) inhibitor is a compound described by Formula I in Appendix B, or a pharmaceutically acceptable salt, solvate, stereoisomer, prodrug, or tautomer thereof.

35. The ~~method~~use of claim 34, wherein the RAS(ON) inhibitor is selected from a compound of Table 1 or Table 2 of Appendix B, or a pharmaceutically acceptable salt, solvate, stereoisomer, prodrug, or tautomer thereof.

36. The ~~method~~use of claim 31, wherein the RAS(ON) inhibitor is a compound described by Formula I in Appendix C, or a pharmaceutically acceptable salt, solvate, stereoisomer, prodrug, or tautomer thereof.

37. The ~~method~~use of claim 36, wherein the RAS(ON) inhibitor is selected from a compound of Table 1 or Table 2 of Appendix C, or a pharmaceutically acceptable salt, solvate, stereoisomer, prodrug, or tautomer thereof.

38. The ~~method~~use of claim 31, wherein the RAS(ON) inhibitor is a compound described by Formula I in Appendix D, or a pharmaceutically acceptable salt, solvate, stereoisomer, prodrug, or tautomer thereof.

39. The ~~method~~use of claim 38, wherein the RAS(ON) inhibitor is selected from a compound of Table 1 or Table 1-1 of Appendix D, or a pharmaceutically acceptable salt, solvate, stereoisomer, prodrug, or tautomer thereof.

40. The ~~method~~use of claim 31, wherein the RAS(ON) inhibitor is selected from the group consisting of RAS-(D), RAS-(E), or a pharmaceutically acceptable salt, solvate, stereoisomer, prodrug, or tautomer thereof, and a combination thereof.

41. The ~~method~~use of any one of claims 25 through 27, wherein the RAS inhibitor is a RAS(OFF) inhibitor.

42. The ~~method~~use of claim 41, wherein the RAS(OFF) inhibitor selectively targets RAS G12C.

43. The ~~method~~use of claim 42, wherein the RAS(OFF) inhibitor is selected from the group consisting of sotorasib (AMG 510), adagrasib (MRTX849), MRTX1257, JNJ-74699157 (ARS-3248), LY3537982, ARS-853, ARS-1620, GDC-6036, BPI-421286, JDQ443, and JAB-21000, or a pharmaceutically acceptable salt, solvate, stereoisomer, prodrug, or tautomer thereof.

44. The ~~method~~use of any one of claims 25 through 27, wherein the RAS inhibitor selectively targets RAS G12D.

45. The ~~method~~use of claim 44, wherein the RAS inhibitor is MRTX1133 or a pharmaceutically acceptable salt, solvate, stereoisomer, prodrug, or tautomer thereof.

46. The ~~method~~use of any one of claims 1 through 24, ~~further comprising administering~~wherein the SOS1 inhibitor is to be administered to the subject, ~~a therapeutically effective amount of~~ and wherein a MEK inhibitor is to be further administered to the subject.

47. The ~~method~~use of claim 46, wherein the MEK inhibitor is pimasertib, selumetinib, cobimetinib, trametinib or binimetinib.

48. The ~~method~~use of any one of claims 1 through 24, ~~further comprising administering~~ wherein the SOS1 inhibitor is to be administered to the subject, ~~a therapeutically effective amount of~~and wherein a CDK4/6 inhibitor is to be further administered to the subject.

49. The ~~method~~use of claim 48, wherein the CDK4/6 inhibitor is abemaciclib, ribociclib, or Palbociclib.

50. The ~~method~~use of any one of claims 1 through 24, ~~further comprising administering~~ wherein the SOS1 inhibitor is to be administered to the subject, ~~a therapeutically effective amount of~~and wherein a PD-1 inhibitor is to be further administered to the subject.

51. The ~~method~~use of claim 50, wherein the PD-1 inhibitor is pembrolizumab, nivolumab, or cemiplimab.

52. The ~~method~~use of any one of claims 1 through 51, wherein the disease or disorder is selected from the group consisting of tumors of hematopoietic and lymphoid system; a myeloproliferative syndrome; a myelodysplastic syndrome; leukemia; acute myeloid leukemia; acute B-lymphoblastic leukemia-lymphoma, juvenile myelomonocytic leukemia; esophageal cancer; breast cancer; lung cancer; colon cancer; gastric cancer; neuroblastoma; bladder cancer; prostate cancer; glioblastoma; urothelial carcinoma; uterine carcinoma; adenoid and ovarian serous cystadenocarcinoma; paraganglioma; pheochromocytoma; pancreatic cancer; adrenocortical carcinoma; stomach adenocarcinoma; sarcoma; rhabdomyosarcoma; lymphoma; head and neck cancer; skin cancer; peritoneum cancer; intestinal cancer; thyroid cancer; endometrial cancer; cancer of the biliary tract; soft tissue cancer; ovarian cancer; central nervous system cancer; stomach cancer; pituitary cancer; genital tract cancer; urinary tract cancer; salivary gland cancer; cervical cancer; liver cancer; eye cancer; cancer of the adrenal gland; cancer of autonomic ganglia; cancer of the upper aerodigestive tract; bone cancer; testicular cancer; pleura cancer; kidney cancer; penis cancer; parathyroid cancer; cancer of the meninges; vulvar cancer; and melanoma.

53. The ~~method~~use of any one of claims 1 through 51, wherein the disease or disorder is selected from brain glioblastoma, lung adenocarcinoma, colon adenocarcinoma, bone marrow leukemia, acute myelocytic leukemia (AML), breast carcinoma, unknown primary melanoma, non-small cell lung carcinoma, skin melanoma, breast invasive ductal carcinoma, lung squamous cell carcinoma, unknown primary adenocarcinoma, bone marrow multiple myeloma, gastroesophageal junction adenocarcinoma, bone marrow myelodysplastic syndrome, prostate acinar adenocarcinoma, bladder urothelial (transitional cell) carcinoma, uterus endometrial adenocarcinoma, acute B-lymphoblastic leukemia-lymphoma, stomach adenocarcinoma, and unknown primary carcinoma.

54. The ~~method~~use of any one of claims 1 through 51, wherein the disease or disorder is acute myelocytic leukemia (AML).

55. The ~~method~~use of claim 54, ~~further comprising administering~~wherein the SOS1 inhibitor is to be administered to the subject, ~~a therapeutically effective amount of~~ and wherein an AML therapeutic agent is to be further administered to the subject.

56. The ~~method~~use of claim 54 or claim 55, wherein the SHP2 mutation is at a position selected from the group consisting of G60, D61, A72, E76, G503 and S502, and a combination thereof.

57. The ~~method~~use of any one of claims 1 through 51, wherein the disease or disorder is selected from the group consisting of acute myeloid leukemia (AML), lung adenocarcinoma, non-small cell lung carcinoma, brain glioblastoma, a myelodysplastic syndrome, skin melanoma, breast carcinoma, stomach adenocarcinoma, acute B-lymphoblastic leukemia-lymphoma, and colon adenocarcinoma.

58. The ~~method~~use of any one of claims 1-53 and 57, wherein the SHP2 mutation is at a position selected from the group consisting of G60, D61, E69, A72, E123, Y197, N308, V428, A461, T468, S502, G503, T507, and a combination thereof.

59. The ~~method~~use of any one of claims 1-53 and 58, wherein the SHP2 mutation is selected from the group consisting of G60V, D61G, D61V, D61Y, E69K, E69Q, A72S, A72T, A72V, E123D, N308D, V428M, A461T, A461G, T468M, S502L, S502P, G503A, G503V, T507K, and a combination thereof.

60. The ~~method~~use of any one of claims 1 through 51, wherein the disease or disorder is a RASopathy.

61. The ~~method~~use of any one of claims 1-51 and 60, wherein the SHP2 mutation is at a position selected from the group consisting of T52, I56, Y62, Y63, E69, K70, E139, L261, R265, N308, T468, M504, Q510, and a combination thereof.

62. The ~~method~~use of any one of claims 1-51 and 61, wherein the SHP2 mutation is selected from the group consisting of T52I, I56V, Y62D, Y63D, Y63C, E69K, E69Q, K70R, E139D, L261F, L261H, R265Q, N308D, T468M, M504V, Q510P, Q510H, and a combination thereof.

63. The ~~method~~use of any one of claims 60 through 62, wherein the RASopathy is selected from the group consisting of Neurofibromatosis type 1, Noonan Syndrome, Noonan Syndrome with Multiple Lentigines, Capillary Malformation-Arteriovenous Malformation Syndrome, Costello Syndrome, Cardio-Facio-Cutaneous Syndrome, Legius Syndrome, and Hereditary gingival fibromatosis.

64. The ~~method~~use of any one of claims 1 through 63, ~~further comprising performing~~ wherein a diagnostic test is performed to determine whether the subject has a SHP2 mutation that induces an activated form of SHP2.

65. The ~~method~~use of any one of claims 25 through 64, wherein the RAS inhibitor targets a wild-type RAS protein.

66. The ~~method~~use of any one of claims 25 through 64, wherein the RAS inhibitor targets a RAS protein mutation.

67. The ~~method~~use of claim 66, wherein the RAS protein mutation is at a position selected from the group consisting of G12, G13, Q61, A146, K117, L19, Q22, V14, A59, and a combination thereof.

68. The ~~method~~use of claim 67, wherein the mutation is at a position selected from the group consisting of G12, G13, and Q61, and a combination thereof.

69. The ~~method~~use of claim 68, wherein the mutation is selected from the group consisting of G12C, G12D, G12A, G12S, G12V, G13C, G13D, Q61K, and Q61L, and a combination thereof.

70. The ~~method~~use of any one of claims 25 through 69, wherein the RAS protein is KRAS.