stromal activation and immunosuppression. Thus, PKCζ and PKC ƛ/ι cooperatively suppress serrated tumorigenesis. As such, low levels of PKCζ and PKC ƛ/ι detected in a sample obtained from a subject may be indicative that the subject has, or will develop serrated CRC.

[0008] The present disclosure further provides that serrated tumors in mice from mouse cell lines with deletion of PKCζ and PKC ƛ/ι show increased expression of hyaluronan (HA), and CD44 which is a receptor for HA and a cancer stem cell marker. This increase in hyaluronan is concomitant with a significant decrease in other stem cell markers. These findings suggest that detection of either HA or CD44, or the combination of the HA and CD44, in a sample obtained from a subject may be indicative that the subject has, or will, develop serrated CRC.

[0009] ~~Aspect~~Examples disclosed herein provide methods of treating a subtype of a disease or condition in a subject by administering to the subject a therapeutically effective amount of an inhibitor of programmed death-ligand 1 (PD-L1) activity or expression, provided low levels of expression of PKCζ and PKCƛ/ι are detected in a biological sample obtained from the subject, as compared to levels of expression of PKCζ and PKCƛ/ι in an individual who does not have the disease or condition. In some ~~embodiment~~examples, a high level of expression of hyaluronan is detected in a biological sample obtained from the subject, as compared to a level of expression of hyaluronan in an individual who does not have the subtype of the disease or condition. In some ~~embodiment~~examples, the high level of hyaluronan is detected by an assay comprising polymerase chain reaction (PCR), reverse transcription PCR (RT-PCR), deoxyribonucleic acid (DNA) sequencing, ribonucleic acid (RNA) sequencing, genotyping array, immunohistochemistry, enzyme-linked immunosorbent assay (ELISA), single-molecule array (Simoa), or a combination thereof. In some ~~embodiment~~examples, the high level of expression of hyaluronan comprises ribonucleic acid (RNA), deoxyribonucleic acid (DNA), or protein. In some ~~embodiment~~examples, the expression of PKCζ and PKCƛ/ι that is detected in the biological sample obtained from the subject is indicative of an increase in expression of hyaluronan in the biological sample, as compared to an individual who does not have the subtype of the disease or condition. In some ~~embodiment~~examples, the disease or condition comprises colorectal cancer, pancreatic cancer, inflammatory bowel disease, ulcerative colitis, Crohn's disease, fibrosis, fibrostenosis, or a combination thereof. In some ~~embodiment~~examples, the subtype of the disease or condition comprises a disease or condition characterized by an increase in hyaluronan in the biological sample obtained from the subject, as compared to the individual who does not have the subtype of the disease or condition. In some ~~embodiment~~examples, the subtype of the disease or condition comprises a disease or condition characterized by serrated polyps

in an intestine of the subject. In some ~~embodiment~~examples, the serrated polyps comprise sessile serrated adenomas (SSAs). In some ~~embodiment~~examples, the subtype of the disease or condition comprises a disease or condition characterized by serrated adenocarcinoma. In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises an antibody, or antigen-binding fragment. In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises a small molecule. In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises an antagonist of PD-L1. In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises an antagonist of programmed cell death protein 1 (PD-1). In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises an anti-PD-L1 antibody. In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises an anti-PD-1 antibody. In some ~~embodiment~~examples, the methods further comprise administering to the subject a therapeutically effective amount of an inhibitor of hyaluronan activity or expression. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises an antibody, or antigen-binding fragment. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises a small molecule. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises an inhibitor of hyaluronan-CD44 binding or agonism. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises an antagonist of CD44. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises an antibody inhibitor of CD44 activity or expression. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises a small molecule inhibitor of CD44 activity or expression. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises an agonist of hyaluronidase activity or expression. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises Pegvorhyaluronidase alfa (PVHA). In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises exogenous hyaluronidase. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises recombinant hyaluronidase. In some ~~embodiment~~examples, the methods further comprise administering to the subject a therapeutically effective amount of an inhibitor of transforming growth factor beta 1 (TGF-β1) activity or expression. In some ~~embodiment~~examples, the inhibitor of TGF- β1 activity or expression comprises an antibody, or antigen-binding fragment. In some ~~embodiment~~examples, the inhibitor of TGF- β1 activity or expression comprises a small molecule. In some ~~embodiment~~examples, the inhibitor of TGF- β1 activity or expression comprises a small molecule inhibitor of a receptor of TGF- β1. In some ~~embodiment~~examples, the inhibitor of TGF- β1 activity or expression comprises galunisertib. In some ~~embodiment~~examples, the biological sample comprises

blood, blood plasma, sera, or tissue biopsy. In some ~~embodiment~~examples, the subject is a human. In some ~~embodiment~~examples, the subject is a mammal. In some ~~embodiment~~examples, the low levels of expression of PKCζ and PKCλ/ι are detected by an assay comprising polymerase chain reaction (PCR), reverse transcription PCR (RT-PCR), deoxyribonucleic acid (DNA) sequencing, ribonucleic acid (RNA) sequencing, genotyping array, immunohistochemistry, enzyme-linked immunosorbent assay (ELISA), single-molecule array (Simoa), or a combination thereof. In some ~~embodiment~~examples, the levels of expression of PKCζ and PKCλ/ι comprise ribonucleic acid (RNA), deoxyribonucleic acid (DNA), or protein.

[0010] ~~Aspect~~Examples disclosed herein provide methods of inhibiting or reducing programmed death-ligand 1 (PD-L1) activity or expression in a subject suffering from a disease or condition, comprising: a) identifying the subject as having low levels of expression of PKCζ and PKCλ/ι , as compared to the levels of expression of PKCζ and PKCλ/ι in an individual who does not have the disease or condition; and b) administering to the subject a therapeutically effective amount of an inhibitor of PD-L1 activity or expression. In some ~~embodiment~~examples, the methods further comprise: identifying the subject as having a high level of expression of hyaluronan, as compared to the level of expression of hyaluronan in an individual who does not have the disease or condition. In some ~~embodiment~~examples, n the level of expression of hyaluronan is identified by an assay comprising polymerase chain reaction (PCR), reverse transcription PCR (RT-PCR), deoxyribonucleic acid (DNA) sequencing, ribonucleic acid (RNA) sequencing, genotyping array, immunohistochemistry, enzyme-linked immunosorbent assay (ELISA), single-molecule array (Simoa), or a combination thereof. In some ~~embodiment~~examples, the level of expression of hyaluronan comprises ribonucleic acid (RNA), deoxyribonucleic acid (DNA), or protein. In some ~~embodiment~~examples, the low levels of expression of PKCζ and PKCλ/ι are indicative of an increase in expression of hyaluronan in the subject, as compared to an individual who does not have the disease or condition. In some ~~embodiment~~examples, the disease or condition comprises colorectal cancer (CRC), serrated CRC, pancreatic cancer, inflammatory bowel disease, ulcerative colitis, Crohn's disease, fibrosis, fibrostenosis, or a combination thereof. In some ~~embodiment~~examples, the inhibitor of PD- L1 activity or expression comprises an antibody, or antigen-binding fragment. In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises a small molecule. In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises an antagonist of PD-L1. In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises an antagonist of programmed cell death protein 1 (PD-1). In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises an anti-PD-L1 antibody. In some ~~embodiment~~examples, the

inhibitor of PD-L1 activity or expression comprises an anti-PD-1 antibody. In some ~~embodiment~~examples, the methods further comprise administering to the subject a therapeutically effective amount of an inhibitor of hyaluronan activity or expression. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises a small molecule. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises an inhibitor of hyaluronan-CD44 binding or agonism. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises an antagonist of CD44. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises an antibody inhibitor of CD44 activity or expression. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises a small molecule inhibitor of CD44 activity or expression. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises an agonist of hyaluronidase activity or expression. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises Pegvorhyaluronidase alfa (PVHA). In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises exogenous hyaluronidase. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises recombinant hyaluronidase. In some ~~embodiment~~examples, the methods further comprise administering to the subject a therapeutically effective amount of an inhibitor of transforming growth factor beta 1 (TGF-β1) activity or expression. In some ~~embodiment~~examples, the inhibitor of TGF- β1 activity or expression comprises an antibody, or antigen-binding fragment. In some ~~embodiment~~examples, the inhibitor of TGF- β1 activity or expression comprises a small molecule. In some ~~embodiment~~examples, the inhibitor of TGF- β1 activity or expression comprises a small molecule inhibitor of a receptor of TGF- β1. In some ~~embodiment~~examples, the inhibitor of TGF- β1 activity or expression comprises galunisertib.

[0011] In some ~~embodiment~~examples, the biological sample comprises blood, blood plasma, sera, or tissue biopsy. In some ~~embodiment~~examples, the subject is a human. In some ~~embodiment~~examples, the subject is a mammal. In some ~~embodiment~~examples, the levels of expression of PKCζ and PKCλ/ιare identified by an assay comprising polymerase chain reaction (PCR), reverse transcription PCR (RT-PCR), deoxyribonucleic acid (DNA) sequencing, ribonucleic acid (RNA) sequencing, genotyping array, immunohistochemistry, enzyme-linked immunosorbent assay (ELISA), single-molecule array (Simoa), or a combination thereof. In some ~~embodiment~~examples, the levels of expression of PKCζ and PKCλ/ι comprise ribonucleic acid (RNA), deoxyribonucleic acid (DNA), or protein.

[0012] ~~Aspect~~Examples disclosed herein provide methods of treating a subtype of a disease or condition in a subject by administering to the subject a therapeutically effective amount of an

inhibitor of hyaluronan activity or expression, provided low levels of expression of PKCζ and PKCλ/ι are detected in a biological sample obtained from the subject, as compared to levels of expression of PKCζ and PKCλ/ιin an individual who does not have the disease or condition. In some ~~embodiment~~examples, a high level of hyaluronan is detected in a biological sample obtained from the subject, as compared to the level of expression of hyaluronan in an individual who does not have the subtype of the disease or condition. In some ~~embodiment~~examples, the high level of hyaluronan is detected by an assay comprising polymerase chain reaction (PCR), reverse transcription PCR (RT-PCR), deoxyribonucleic acid (DNA) sequencing, ribonucleic acid (RNA) sequencing, genotyping array, immunohistochemistry, enzyme-linked immunosorbent assay (ELISA), single-molecule array (Simoa), or a combination thereof. In some ~~embodiment~~examples, the levels of expression of PKCζ and PKCλ/ι are detected comprise ribonucleic acid (RNA), deoxyribonucleic acid (DNA), or protein. In some ~~embodiment~~examples, the expression of PKCζ and PCKλ that are detected in the biological sample obtained from the subject are indicative of an increase in expression of hyaluronan in the biological sample, as compared to an individual who does not have the subtype of the disease or condition. In some ~~embodiment~~examples, the disease or condition comprises colorectal cancer, pancreatic cancer, inflammatory bowel disease, ulcerative colitis, Crohn's disease, fibrosis, fibrostenosis, or a combination thereof. In some ~~embodiment~~examples, the subtype of the disease or condition comprises a disease or condition characterized by an increase in hyaluronan in the biological sample obtained from the subject, as compared to the individual who does not have the subtype of the disease or condition. In some ~~embodiment~~examples, the subtype of the disease or condition comprises a disease or condition characterized by serrated polyps in an intestine of the subject. In some ~~embodiment~~examples, the serrated polyps comprise sessile serrated adenomas (SSAs). In some ~~embodiment~~examples, the subtype of the disease or condition comprises a disease or condition characterized by serrated adenocarcinoma. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises a small molecule. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises an inhibitor of hyaluronan-CD44 binding or agonism. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises an antagonist of CD44. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises an antibody inhibitor of CD44 activity or expression. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises a small molecule inhibitor of CD44 activity or expression. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises an agonist of hyaluronidase activity or expression. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises

Pegvorhyaluronidase alfa (PVHA). In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises exogenous hyaluronidase. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises recombinant hyaluronidase. In some ~~embodiment~~examples, the methods further comprise administering to the subject a therapeutically effective amount of an inhibitor of transforming growth factor beta 1 (TGF-β1) activity or expression. In some ~~embodiment~~examples, the inhibitor of TGF- β1 activity or expression comprises an antibody, or antigen-binding fragment. In some ~~embodiment~~examples, the inhibitor of TGF- β1 activity or expression comprises a small molecule. In some ~~embodiment~~examples, the inhibitor of TGF- β1 activity or expression comprises a small molecule inhibitor of a receptor of TGF- β1. In some ~~embodiment~~examples, the inhibitor of TGF- β1 activity or expression comprises galunisertib. In some ~~embodiment~~examples, the methods further comprise administering to the subject a therapeutically effective amount of an inhibitor of programmed death-ligand 1 (PD-L1) activity or expression. In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises an antibody, or antigen-binding fragment. In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises a small molecule. In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises an antagonist of PD-L1. In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises an antagonist of programmed cell death protein 1 (PD-1). In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises an anti-PD-L1 antibody. In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises an anti-PD-1 antibody. In some ~~embodiment~~examples, the biological sample comprises blood, blood plasma, sera, or tissue biopsy. In some ~~embodiment~~examples, the subject is a human. In some ~~embodiment~~examples, the subject is a mammal. In some ~~embodiment~~examples, the levels of expression of PKCζ and PKCλ/ι are detected by an assay comprising polymerase chain reaction (PCR), reverse transcription PCR (RT-PCR), deoxyribonucleic acid (DNA) sequencing, ribonucleic acid (RNA) sequencing, genotyping array, immunohistochemistry, enzyme-linked immunosorbent assay (ELISA), single-molecule array (Simoa), or a combination thereof. In some ~~embodiment~~examples, the levels of expression of PKCζ and PKCλ/ι comprise ribonucleic acid (RNA), deoxyribonucleic acid (DNA), or protein.

[0013] ~~Aspect~~Examples disclosed herein provide methods of inhibiting or reducing hyaluronan activity or expression in a subject suffering from a disease or condition, comprising: a) identifying the subject as having low levels of expression of PKCζ and PKCλ/ι , as compared to the levels of expression of PKCζ and PKCλ/ι in an individual who does not have the disease or condition; and b) administering to the subject a therapeutically effective amount of

an inhibitor of hyaluronan activity or expression. In some ~~embodiment~~examples, the methods further comprise: identifying the subject as having a high level of expression of hyaluronan, as compared to the level of expression of hyaluronan in an individual who does not have the disease or condition. In some ~~embodiment~~examples, the level of expression of hyaluronan is identified by an assay comprising polymerase chain reaction (PCR), reverse transcription PCR (RT-PCR), deoxyribonucleic acid (DNA) sequencing, ribonucleic acid (RNA) sequencing, genotyping array, immunohistochemistry, enzyme-linked immunosorbent assay (ELISA), single-molecule array (Simoa), or a combination thereof. In some ~~embodiment~~examples, the high level of expression of hyaluronan comprises ribonucleic acid (RNA), deoxyribonucleic acid (DNA), or protein. In some ~~embodiment~~examples, the low levels of expression of PKCζ and PKCλ/ι are indicative of an increase in expression of hyaluronan in the subject, as compared to an individual who does not have the disease or condition. In some ~~embodiment~~examples, the disease or condition comprises colorectal cancer (CRC), serrated CRC, pancreatic cancer, inflammatory bowel disease, ulcerative colitis, Crohn's disease, fibrosis, fibrostenosis, or a combination thereof. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises a small molecule. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises an inhibitor of hyaluronan-CD44 binding or agonism. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises an antagonist of CD44. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises an antibody inhibitor of CD44 activity or expression. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises a small molecule inhibitor of CD44 activity or expression. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises an agonist of hyaluronidase activity or expression. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises Pegvorhyaluronidase alfa (PVHA). In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises exogenous hyaluronidase. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises recombinant hyaluronidase. In some ~~embodiment~~examples, the methods further comprise administering to the subject a therapeutically effective amount of an inhibitor of transforming growth factor beta 1 (TGF-β1) activity or expression. In some ~~embodiment~~examples, the inhibitor of TGF-β1 activity or expression comprises an antibody, or antigen-binding fragment. In some ~~embodiment~~examples, the inhibitor of TGF- β1 activity or expression comprises a small molecule. In some ~~embodiment~~examples, the inhibitor of TGF- β1 activity or expression comprises a small molecule inhibitor of a receptor of TGF- β1. In some ~~embodiment~~examples, the inhibitor of TGF- β1 activity or expression comprises

galunisertib. In some ~~embodiment~~examples, the methods further comprise administering to the subject a therapeutically effective amount of an inhibitor of programmed death-ligand 1 (PD- L1) activity or expression. In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises an antibody, or antigen-binding fragment. In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises a small molecule. In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises an antagonist of PD-L1. In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises an antagonist of programmed cell death protein 1 (PD-1). In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises an anti-PD-L1 antibody. In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises an anti-PD-1 antibody. In some ~~embodiment~~examples, the biological sample comprises blood, blood plasma, sera, or tissue biopsy. In some ~~embodiment~~examples, the subject is a human. In some ~~embodiment~~examples, the subject is a mammal. In some ~~embodiment~~examples, the levels of expression of PKCζ and PKCλ/ι are identified by an assay comprising polymerase chain reaction (PCR), reverse transcription PCR (RT-PCR), deoxyribonucleic acid (DNA) sequencing, ribonucleic acid (RNA) sequencing, genotyping array, immunohistochemistry, enzyme-linked immunosorbent assay (ELISA), single- molecule array (Simoa), or a combination thereof. In some ~~embodiment~~examples, the levels of expression of PKCζ and PKCλ/ι comprise ribonucleic acid (RNA), deoxyribonucleic acid (DNA), or protein. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises an antibody, or antigen-binding fragment. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises a small molecule. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises an inhibitor of hyaluronan-CD44 binding or agonism. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises an antagonist of CD44. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises an antibody inhibitor of CD44 activity or expression. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises a small molecule inhibitor of CD44 activity or expression. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises an agonist of hyaluronidase activity or expression. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises Pegvorhyaluronidase alfa (PVHA). In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises exogenous hyaluronidase. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises recombinant hyaluronidase.

[0014] ~~Aspect~~Examples disclosed herein provide methods of ameliorating or preventing tumorigenesis in a subject with serrated colorectal cancer (CRC) by administering to the

subject a therapeutically effective amount of an inhibitor of hyaluronan activity or expression, provided low levels of expression of PKCζ and PKCλ/ι are detected in a biological sample obtained from the subject, as compared to levels of expression of PKCζ and PKCλ/ι in an individual who does not have serrated CRC. In some ~~embodiment~~examples, a high level of expression of hyaluronan is detected in a biological sample obtained from the subject, as compared to a level of expression of hyaluronan in an individual who does not have the CRC. In some ~~embodiment~~examples, the high level of expression of hyaluronan is detected by an assay comprising polymerase chain reaction (PCR), reverse transcription PCR (RT-PCR), deoxyribonucleic acid (DNA) sequencing, ribonucleic acid (RNA) sequencing, genotyping array, immunohistochemistry, enzyme-linked immunosorbent assay (ELISA), single-molecule array (Simoa), or a combination thereof. In some ~~embodiment~~examples, the high level of expression of hyaluronan comprises ribonucleic acid (RNA), deoxyribonucleic acid (DNA), or protein. In some ~~embodiment~~examples, the low levels of expression of PKCζ and PCKλ that are detected in the biological sample obtained from the subject are indicative of an increase in expression of hyaluronan in the biological sample, as compared to an individual who does not have the serrated CRC. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises a small molecule. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises an inhibitor of hyaluronan-CD44 binding or agonism. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises an antagonist of CD44. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises an antibody inhibitor of CD44 activity or expression. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises a small molecule inhibitor of CD44 activity or expression. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises an agonist of hyaluronidase activity or expression. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises Pegvorhyaluronidase alfa (PVHA). In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises exogenous hyaluronidase. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises recombinant hyaluronidase. In some ~~embodiment~~examples, the methods further comprise administering to the subject a therapeutically effective amount of an inhibitor of transforming growth factor beta 1 (TGF-β1) activity or expression. In some ~~embodiment~~examples, the inhibitor of TGF- β1 activity or expression comprises an antibody, or antigen-binding fragment. In some ~~embodiment~~examples, the inhibitor of TGF- β1 activity or expression comprises a small molecule. In some ~~embodiment~~examples, the inhibitor of TGF- β1 activity or expression comprises a small molecule inhibitor of a receptor of TGF-

β1. In some ~~embodiment~~examples, the inhibitor of TGF- β1 activity or expression comprises galunisertib. In some ~~embodiment~~examples, the methods further comprise administering to the subject a therapeutically effective amount of an inhibitor of programmed death-ligand 1 (PD- L1) activity or expression. In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises an antibody, or antigen-binding fragment. In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises a small molecule. In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises an antagonist of PD-L1. In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises an antagonist of programmed cell death protein 1 (PD-1). In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises an anti-PD-L1 antibody. In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises an anti-PD-1 antibody. In some ~~embodiment~~examples, the biological sample comprises blood, blood plasma, sera, or tissue biopsy. In some ~~embodiment~~examples, the subject is a human. In some ~~embodiment~~examples, the subject is a mammal. In some ~~embodiment~~examples, the low levels of expression of PKCζ and PKCλ/ι are detected by an assay comprising polymerase chain reaction (PCR), reverse transcription PCR (RT-PCR), deoxyribonucleic acid (DNA) sequencing, ribonucleic acid (RNA) sequencing, genotyping array, immunohistochemistry, enzyme-linked immunosorbent assay (ELISA), single-molecule array (Simoa), or a combination thereof. In some ~~embodiment~~examples, the levels of expression of PKCζ and PKCλ/ι comprise ribonucleic acid (RNA), deoxyribonucleic acid (DNA), or protein.

[0015] ~~Aspect~~Examples disclosed herein provide methods of ameliorating or preventing tumorigenesis in a subject with serrated colorectal cancer (CRC) by, the method comprising: a) identifying the subject as having low levels of expression of PKCζ and PKCλ/ι , as compared to the levels of expression of PKCζ and PKCλ/ι in an individual who does not have the serrated CRC; and b) administering to the subject a therapeutically effective amount of an inhibitor of hyaluronan activity or expression. In some ~~embodiment~~examples, the methods further comprise: identifying the subject as having a high level of expression of hyaluronan, as compared to the level of expression of hyaluronan in an individual who does not have the CRC. In some ~~embodiment~~examples, the high level of expression of hyaluronan is identified by an assay comprising polymerase chain reaction (PCR), reverse transcription PCR (RT-PCR), deoxyribonucleic acid (DNA) sequencing, ribonucleic acid (RNA) sequencing, genotyping array, immunohistochemistry, enzyme-linked immunosorbent assay (ELISA), single-molecule array (Simoa), or a combination thereof. In some ~~embodiment~~examples, the level of expression of hyaluronan comprises ribonucleic acid (RNA), deoxyribonucleic acid (DNA),

or protein. In some ~~embodiment~~examples, the low levels of expression of PKCζ and PKCλ/ι are indicative of an increase in expression of hyaluronan in the subject, as compared to an individual who does not have the disease or condition. In some ~~embodiment~~examples, the biological sample comprises blood, blood plasma, sera, or tissue biopsy. In some ~~embodiment~~examples, the subject is a human. In some ~~embodiment~~examples, the subject is a mammal. In some ~~embodiment~~examples, the levels of expression of PKCζ and PKCλ/ι are identified by an assay comprising polymerase chain reaction (PCR), reverse transcription PCR (RT-PCR), deoxyribonucleic acid (DNA) sequencing, ribonucleic acid (RNA) sequencing, genotyping array, immunohistochemistry, enzyme-linked immunosorbent assay (ELISA), single-molecule array (Simoa), or a combination thereof. In some ~~embodiment~~examples, the levels of expression of PKCζ and PKCλ/ι comprise ribonucleic acid (RNA), deoxyribonucleic acid (DNA), or protein. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises an antibody, or antigen-binding fragment. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises a small molecule. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises an inhibitor of hyaluronan-CD44 binding or agonism. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises an antagonist of CD44. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises an antibody inhibitor of CD44 activity or expression. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises a small molecule inhibitor of CD44 activity or expression. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises an agonist of hyaluronidase activity or expression. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises Pegvorhyaluronidase alfa (PVHA). In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises exogenous hyaluronidase. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises recombinant hyaluronidase. In some ~~embodiment~~examples, the methods further comprise administering to the subject a therapeutically effective amount of an inhibitor of transforming growth factor beta 1 (TGF-β1) activity or expression. In some ~~embodiment~~examples, the inhibitor of TGF- β1 activity or expression comprises an antibody, or antigen-binding fragment. In some ~~embodiment~~examples, the inhibitor of TGF- β1 activity or expression comprises a small molecule. In some ~~embodiment~~examples, the inhibitor of TGF- β1 activity or expression comprises a small molecule inhibitor of a receptor of TGF- β1. In some ~~embodiment~~examples, the inhibitor of TGF- β1 activity or expression comprises galunisertib. In some ~~embodiment~~examples, the methods further comprise administering to the subject a therapeutically effective amount of an inhibitor of programmed death-ligand 1 (PD-

L1) activity or expression. In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises an antibody, or antigen-binding fragment. In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises a small molecule. In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises an antagonist of PD-L1. In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises an antagonist of programmed cell death protein 1 (PD-1). In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises an anti-PD-L1 antibody. In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises an anti-PD-1 antibody.

[0016] ~~Aspect~~Examples disclosed herein provide methods of diagnosing a subtype of colorectal cancer (CRC) in a subject in need thereof, the method comprising: a)obtaining a biological sample from a subject in need thereof; b) subjecting the biological sample to an assay suitable to detect levels of expression of PKCζ and PKCλ/ι ; and c) diagnosing the subject with serrated colorectal cancer (CRC), provided the levels of expression of PKCζ and PKCλ/ι detected in the biological sample obtained from the subject are low, as compared to levels of expression of PKCζ and PKCλ/ι in an individual that does not have the CRC. In some ~~embodiment~~examples, the methods further comprise: a) subjecting the biological sample to an assay suitable to detect a colon cancer subtype (CCS), the CCS comprising chromosomal unstable phenotype (CCS1), microsatellite instability-high and CpG island methylator phenotypes (MSI/CIMP+), or microsatellite stable phenotype (MSS); and b) diagnosing the subject with serrated CRC, provided the CCS detected comprises the MSS phenotype. In some ~~embodiment~~examples, the low levels of expression of PKCζ and PKCλ/ι are indicative of an increase in expression of hyaluronan in the subject, as compared to an individual who does not have the disease or condition. In some ~~embodiment~~examples, the biological sample comprises blood, blood plasma, sera, or tissue biopsy. In some ~~embodiment~~examples, the subject is a human. In some ~~embodiment~~examples, the subject is a mammal. In some ~~embodiment~~examples, the assay suitable to detect the levels of expression of PKCζ and PKCλ/ι comprises polymerase chain reaction (PCR), reverse transcription PCR (RT-PCR), deoxyribonucleic acid (DNA) sequencing, ribonucleic acid (RNA) sequencing, genotyping array, immunohistochemistry, enzyme-linked immunosorbent assay (ELISA), single-molecule array (Simoa), or a combination thereof. In some ~~embodiment~~examples, the levels of expression of PKCζ and PKCλ/ι comprise ribonucleic acid (RNA), deoxyribonucleic acid (DNA), or protein. In some ~~embodiment~~examples, the methods further comprise treating the subject by administering a therapeutically effective amount of an inhibitor of transforming growth factor beta 1 (TGF-β1) activity or expression, provided the subject is diagnosed with serrated CRC. In some ~~embodiment~~examples, the inhibitor of

TGF- β1 activity or expression comprises an antibody, or antigen-binding fragment. In some ~~embodiment~~examples, the inhibitor of TGF- β1 activity or expression comprises a small molecule. In some ~~embodiment~~examples, the inhibitor of TGF- β1 activity or expression comprises a small molecule inhibitor of a receptor of TGF- β1. In some ~~embodiment~~examples, the inhibitor of TGF- β1 activity or expression comprises galunisertib. In some ~~embodiment~~examples, the methods further comprise treating the subject by administering a therapeutically effective amount of an inhibitor of hyaluronan activity or expression, provided the subject is diagnosed with serrated CRC. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises an antibody, or antigen-binding fragment. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises a small molecule. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises an inhibitor of hyaluronan-CD44 binding or agonism. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises an antagonist of CD44. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises an antibody inhibitor of CD44 activity or expression. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises a small molecule inhibitor of CD44 activity or expression. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises an agonist of hyaluronidase activity or expression. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises Pegvorhyaluronidase alfa (PVHA). In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises exogenous hyaluronidase. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises recombinant hyaluronidase. In some ~~embodiment~~examples, the methods further comprise treating the subject by administering a therapeutically effective amount of an inhibitor of programmed death-ligand 1 (PD-L1) activity or expression, provided the subject is diagnosed with serrated CRC. In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises an antibody, or antigen-binding fragment. In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises a small molecule. In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises an antagonist of PD-L1. In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises an antagonist of programmed cell death protein 1 (PD-1). In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises an anti-PD-L1 antibody. In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises an anti-PD-1 antibody.

[0017] ~~Aspect~~Examples disclosed herein provide methods of characterizing a subtype of colorectal cancer (CRC) in a subject, the method comprising: a) obtaining a biological sample

from a subject with colorectal cancer (CRC); b) subjecting the biological sample to an assay suitable to detect levels of expression of PKCζ and PKCλ/ι ; and c) characterizing the CRC as serrated CRC, provided the levels of expression of PKCζ and PKCλ/ι detected in the biological sample obtained from the subject are low, as compared to the levels of expression of PKCζ and PKCλ/ι in an individual that does not have the CRC. In some ~~embodiment~~examples, the methods further comprise: a) subjecting the biological sample to an assay suitable to detect a colon cancer subtype (CCS), the CCS comprising chromosomal unstable phenotype (CCS1), microsatellite instability-high and CpG island methylator phenotypes (MSI/CIMP+), or microsatellite stable phenotype (MSS); and b) characterizing the subtype of CRC as serrated CRC, provided the CCS detected comprises the MSS phenotype. In some ~~embodiment~~examples, the low levels of expression of PKCζ and PKCλ/ι are indicative of an increase in expression of hyaluronan in the subject, as compared to an individual who does not have the disease or condition. In some ~~embodiment~~examples, the biological sample comprises blood, blood plasma, sera, or tissue biopsy. In some ~~embodiment~~examples, the subject is a human. In some ~~embodiment~~examples, the subject is a mammal. In some ~~embodiment~~examples, the assay suitable to detect the levels of expression of PKCζ and PKCλ/ι comprises polymerase chain reaction (PCR), reverse transcription PCR (RT-PCR), deoxyribonucleic acid (DNA) sequencing, ribonucleic acid (RNA) sequencing, genotyping array, immunohistochemistry, enzyme-linked immunosorbent assay (ELISA), single-molecule array (Simoa), or a combination thereof. In some ~~embodiment~~examples, the levels of expression of PKCζ and PKCλ/ι comprise ribonucleic acid (RNA), deoxyribonucleic acid (DNA), or protein. In some ~~embodiment~~examples, the methods further comprise treating the subject by administering a therapeutically effective amount of an inhibitor of transforming growth factor beta 1 (TGF-β1) activity or expression, provided the CRC is characterized as serrated CRC. In some ~~embodiment~~examples, the inhibitor of TGF- β1 activity or expression comprises an antibody, or antigen-binding fragment. In some ~~embodiment~~examples, the inhibitor of TGF- β1 activity or expression comprises a small molecule. In some ~~embodiment~~examples, the inhibitor of TGF- β1 activity or expression comprises a small molecule inhibitor of a receptor of TGF- β1. In some ~~embodiment~~examples, the inhibitor of TGF- β1 activity or expression comprises galunisertib. In some ~~embodiment~~examples, the methods further comprise treating the subject by administering a therapeutically effective amount of an inhibitor of hyaluronan activity or expression, provided the CRC is characterized as serrated CRC. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises an antibody, or antigen-binding fragment. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises a small molecule. In some ~~embodiment~~examples, the inhibitor of

hyaluronan activity or expression comprises an inhibitor of hyaluronan-CD44 binding or agonism. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises an antagonist of CD44. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises an antibody inhibitor of CD44 activity or expression. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises a small molecule inhibitor of CD44 activity or expression. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises an agonist of hyaluronidase activity or expression. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises Pegvorhyaluronidase alfa (PVHA). In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises exogenous hyaluronidase. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises recombinant hyaluronidase. In some ~~embodiment~~examples, the methods further comprise treating the subject by administering a therapeutically effective amount of an inhibitor of programmed death-ligand 1 (PD-L1) activity or expression, provided the CRC is characterized as being serrated CRC. In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises an antibody, or antigen-binding fragment. In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises a small molecule. In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises an antagonist of PD-L1. In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises an antagonist of programmed cell death protein 1 (PD-1). In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises an anti-PD-L1 antibody. In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises an anti-PD-1 antibody.

[0018] ~~Aspect~~Examples disclosed herein provide methods of determining whether a subject suffering from an inflammatory bowel disease (IBD) has, or will, develop serrated colorectal cancer (CRC), the method comprising: a) obtaining a biological sample from the subject; b) subjecting the biological sample to an assay suitable to detect levels of expression of PKCζ and PKCλ/ι ; and c) determining that the subject has, or will develop, serrated CRC, provided the levels of expression of PKCζ and PKCλ/ι detected in the biological sample obtained from the subject are low, as compared to levels of expression of PKCζ and PKCλ/ι in an individual that does not have CRC. In some ~~embodiment~~examples, the IBD comprises Crohn's disease, ulcerative colitis, medically refractory ulcerative colitis, medically refractory or complicated form of Crohn's disease, colitis, fibrosis, fibrostenosis, or a combination thereof. In some ~~embodiment~~examples, the low levels of expression of PKCζ and PKCλ/ι are indicative of an increase in expression of hyaluronan in the subject, as compared to an

individual who does not have the disease or condition. In some ~~embodiment~~examples, the biological sample comprises blood, blood plasma, sera, or tissue biopsy. In some ~~embodiment~~examples, the subject is a human. In some ~~embodiment~~examples, the subject is a mammal. In some ~~embodiment~~examples, the assay suitable to detect levels of expression of PKCζ and PKCλ/ι comprises polymerase chain reaction (PCR), reverse transcription PCR (RT-PCR), deoxyribonucleic acid (DNA) sequencing, ribonucleic acid (RNA) sequencing, genotyping array, immunohistochemistry, enzyme-linked immunosorbent assay (ELISA), single-molecule array (Simoa), or a combination thereof. In some ~~embodiment~~examples, the levels of expression of PKCζ and PKCλ/ι comprise ribonucleic acid (RNA), deoxyribonucleic acid (DNA), or protein. In some ~~embodiment~~examples, the methods further comprise treating the subject by administering a therapeutically effective amount of an inhibitor of transforming growth factor beta 1 (TGF- β1) activity or expression, provided the subject is determined to have, or will develop, serrated CRC. In some ~~embodiment~~examples, in the inhibitor of TGF- β1 activity or expression comprises an antibody, or antigen-binding fragment. In some ~~embodiment~~examples, the inhibitor of TGF- β1 activity or expression comprises a small molecule. In some ~~embodiment~~examples, the inhibitor of TGF- β1 activity or expression comprises a small molecule inhibitor of a receptor of TGF- β1. In some ~~embodiment~~examples, the inhibitor of TGF- β1 activity or expression comprises galunisertib. In some ~~embodiment~~examples, the methods further comprise treating the subject by administering a therapeutically effective amount of an inhibitor of hyaluronan activity or expression, provided the subject is determined to have, or will develop, serrated CRC. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises an antibody, or antigen-binding fragment. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises a small molecule. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises an inhibitor of hyaluronan-CD44 binding or agonism. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises an antagonist of CD44. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises an antibody inhibitor of CD44 activity or expression. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises a small molecule inhibitor of CD44 activity or expression. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises an agonist of hyaluronidase activity or expression. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises Pegvorhyaluronidase alfa (PVHA). In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises exogenous hyaluronidase. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises recombinant hyaluronidase. In some

~~embodiment~~examples, the methods further comprise treating the subject by administering a therapeutically effective amount of an inhibitor of programmed death-ligand 1 (PD-L1) activity or expression, provided the subject is determined to have, or will develop, serrated CRC. In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises an antibody, or antigen-binding fragment. In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises a small molecule. In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises an antagonist of PD-L1. In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises an antagonist of programmed cell death protein 1 (PD-1). In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises an anti-PD-L1 antibody. In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises an anti-PD-1 antibody.

[0019] ~~Aspect~~Examples disclosed herein provide models of serrated colorectal cancer comprising: a) a quantity of cells that do not express, or underexpress, PKCζ and PKCλ/ι ; b) an animal that has been injected with the quantity of the cells that do not express, or underexpress, PKCζ and PKCλ/ι ; or c) a transgenic animal with a transgene comprising a knockout or knockdown of Prkci and Prkcz. In some ~~embodiment~~examples, the quantity of cells and the transgenic animal are further characterized by a microsatellite stable phenotype. In some ~~embodiment~~examples, the quantity of cells and the transgenic animal are enriched for an expression of one or more genes in the Extracellular Signal-Regulated Kinase (ERK) pathway and/or Yes Associated Protein (YAP) pathway. In some ~~embodiment~~examples, the quantity of cells exhibit lower cell death, as compared to a quantity of cells that do not express, or underexpress, PKCζ or PKCλ/ι . In some ~~embodiment~~examples, the transgenic animal exhibits lower cell death, as compared to a transgenic animal with a transgene comprising a knockout or knockdown of Prkci or Prkcz. In some ~~embodiment~~examples, the quantity of cells overexpress hyaluronan. In some ~~embodiment~~examples, the transgenic animal overexpresses hyaluronan in stroma of serrated tumors of the transgenic animal. In some ~~embodiment~~examples, the quantity of cells overexpress CD44. In some ~~embodiment~~examples, the transgenic animal overexpresses CD44. In some ~~embodiment~~examples, the quantity of cells underexpress stem cell biomarkers comprising Olfm4, Ascl2, or Lgr5. In some ~~embodiment~~examples, the transgenic animal underexpresses a stem cell biomarker comprising Olfm4, Ascl2, or Lgr5. In some ~~embodiment~~examples, the transgenic animal underexpresses an interferon-responsive gene comprising Irf7, Oas1a, Isg15, or Cxcl10. In some ~~embodiment~~examples, the quantity of cells underexpresses an interferon-responsive gene comprising Irf7, Oas1a, Isg15, or Cxcl10. In some ~~embodiment~~examples, the transgenic animal comprises a mammal. In some ~~embodiment~~examples, the transgenic animal comprises a mouse. In some ~~embodiment~~examples, the

transgenic animal comprises a rat. In some ~~embodiment~~examples, the transgenic animal comprises a monkey. In some ~~embodiment~~examples, the quantity of cells comprises an organoid. In some ~~embodiment~~examples, the quantity of cells comprises a 3D culture. In some ~~embodiment~~examples, the transgenic animal is produced by breeding a first animal comprising a transgene encoding a recombinase operably linked to a ubiquitous promoter in villus and crypt epithelial cells of a small and a large intestine, and a second animal comprising a loxP-flanked genes comprising Prkci and Prkcz, to produce a transgenic animal with a knockout or knockdown of Prkci and Prkcz, respectively, the villus and the crypt epithelial cells of the small and the large intestine. In some ~~embodiment~~examples, the ubiquitous promoter comprises a vasa promoter, c-kit promoter, Dnd1 promoter, Dppa3 promoter, Fkbp6 promoter, Fragilis promoter, Fragilis-2 promoter, GDF-3 promoter, Mov10l1 promoter, Nanog promoter, Nanos2 promoter, Nanos3 promoter, oct3/4 promoter, Prdm1 promoter, Prdm14 promoter, Tex13 promoter, Tiar promoter or TNAP promoter.

[0020] ~~Aspect~~Examples disclosed herein provide methods of screening for modulators of serrated tumorigenesis, the method comprising: a) providing the model of serrated colorectal cancer disclosed herein b) contacting the model with a putative modulator of tumorigenesis; and c) detecting one or more changes in one or more tumor-associated parameters in the model. In some ~~embodiment~~examples, the tumor-associated parameter comprises recruitment of CD8+ T cells to a serrated tumor, progression of a sessile serrated adenoma (SSA)to adenocarcinoma, a number of serrated tumors, a size of serrated tumors, a total load of serrated tumors, an increase in an expression of alpha-smooth muscle actin (αSMA), or collagen deposition, or a combination thereof. In some ~~embodiment~~examples, the putative modulator negatively modulates tumorigenesis, provided an increase in CD8+ T cells to a serrated tumor is observed. In some ~~embodiment~~examples, the putative modulator negatively modulates tumorigenesis, provided the progression of the SSA to adenocarcinoma is not observed. In some ~~embodiment~~examples, the putative modulator negatively modulates tumorigenesis, provided that a decrease in a number of serrated tumors, as compared to the number of serrated tumors in the model before contacting the model with the putative modulator, is observed. In some ~~embodiment~~examples, the putative modulator negatively modulates tumorigenesis, provided that a reduction in a size of serrated tumor, as compared to the size of serrated tumors in the model before contacting the model with the putative modulator, is observed. In some ~~embodiment~~examples, the putative modulator negatively modulates tumorigenesis, provided that a decrease in a total load of serrated tumors, as compared to the total load of serrated tumors in the model before contacting the model with the putative modulator, is observed. In some ~~embodiment~~examples, the

putative modulator negatively modulates tumorigenesis, provided that an increase in expression of αSMA, as compared to the expression of αSMA in the model before contacting the model with the putative modulator, is not observed. In some ~~embodiment~~examples, the putative modulator negatively modulates tumorigenesis, provided than an increase in collagen deposition in the model, as compared to collagen deposition in the model before contacting the model with the putative modulator, is not observed. In some ~~embodiment~~examples, the putative modulator is selected from the group consisting of an inhibitor of programmed death-ligand 1 (PD-L1) activity or expression, an inhibitor of transforming growth factor beta 1 (TGF-β1) activity or expression, and an inhibitor of hyaluronan activity or expression. In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises an antibody, or antigen-binding fragment. In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises a small molecule. In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises an antagonist of PD-L1. In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises an antagonist of programmed cell death protein 1 (PD-1). In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises an anti-PD-L1 antibody. In some ~~embodiment~~examples, the inhibitor of PD-L1 activity or expression comprises an anti-PD-1 antibody. In some ~~embodiment~~examples, in the inhibitor of hyaluronan activity or expression comprises an antibody, or antigen-binding fragment. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises a small molecule. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises an inhibitor of hyaluronan-CD44 binding or agonism. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises an antagonist of CD44. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises an antibody inhibitor of CD44 activity or expression. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises a small molecule inhibitor of CD44 activity or expression. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises an agonist of hyaluronidase activity or expression. In some ~~embodiment~~examples, n the inhibitor of hyaluronan activity or expression comprises Pegvorhyaluronidase alfa (PVHA). In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises exogenous hyaluronidase. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises recombinant hyaluronidase. In some ~~embodiment~~examples, the inhibitor of TGF- β1 activity or expression comprises an antibody, or antigen-binding fragment. In some ~~embodiment~~examples, the inhibitor of TGF- β1 activity or expression comprises a small molecule. In some ~~embodiment~~examples, the inhibitor of TGF- β1 activity or expression comprises a small molecule inhibitor of a receptor

of TGF- β1. In some ~~embodiment~~examples, the inhibitor of TGF- β1 activity or expression comprises galunisertib.

[0021] ~~Aspect~~Examples disclosed herein provide methods of producing an animal model of serrated colorectal cancer comprising: a) providing an animal that is Prkci fl/fl and Prkcz fl/fl, wherein the animal has loxP sites flanking genes comprising Prkci and Prkcz; and b) crossing the animal that is Prkci fl/fl and Prkcz fl/fl with an animal expressing a Cre recombinase operably linked to an ubiquitous promoter in villus and crypt epithelial cells of a small and a large intestine, thereby generating a transgenic animal with deletions in Pkcζ and PKCλ/ι in the villus and the crypt epithelial cells of the small and the large intestine. In some ~~embodiment~~examples, the animal model comprises a mammal. In some ~~embodiment~~examples, the animal model comprises a mouse. In some ~~embodiment~~examples, the animal model comprises a rat. In some ~~embodiment~~examples, the animal model comprises a monkey. In some ~~embodiment~~examples, the animal model is characterized by a microsatellite stable phenotype. In some ~~embodiment~~examples, the animal model is enriched for an expression of one or more genes in the Extracellular Signal-Regulated Kinase (ERK) pathway and/or Yes Associated Protein (YAP) pathway. In some ~~embodiment~~examples, the animal model exhibits lower cell death, as compared to an animal that does not express, or underexpress, PKCζ or PKCλ/ι . In some ~~embodiment~~examples, the animal model exhibits lower cell death, as compared to an animal with a transgene comprising a knockout or knockdown of Prkci or Prkcz. In some ~~embodiment~~examples, the animal model overexpresses hyaluronan in stroma of serrated tumors of the animal. In some ~~embodiment~~examples, the animal model overexpresses CD44, as compared to a normal animal. In some ~~embodiment~~examples, the animal model underexpresses a stem cell biomarker comprising Olfm4, Ascl2, or Lgr5, as compared to a normal animal. In some ~~embodiment~~examples, the animal model underexpresses an interferon-responsive gene comprising Irf7, Oas1a, Isg15, or Cxcl10, as compared to a normal animal.

[0022] ~~Aspect~~Examples disclosed herein also provide a method of treating a serrated tumor in a subject. The method includes a step of administering to the subject a therapeutically effective amount of an inhibitor of hyaluronan activity or expression, wherein a biological sample from the subject has low levels of expression of PKCζ and PKCλ/ι compared to levels of expression of PKCζ and PKCλ/ι in an individual without a serrated tumor. In one aspect, the present disclosure refers to use of a therapeutically effective amount of an inhibitor of hyaluronan activity or expression in the manufacture of a medicament for treating a serrated tumor in a subject, wherein a biological sample from the subject has lower levels of expression of PKCζ and PKC λ/ι compared to levels of expression of PKCζ and PKC λ/ι in an individual without a serrated tumor. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises a small molecule. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises an inhibitor of hyaluronan-CD44 binding or agonism. Alternatively and/or additionally, the inhibitor of hyaluronan activity or expression comprises an antagonist of CD44. In some

instances, the inhibitor of hyaluronan activity or expression comprises an antibody inhibitor of CD44 activity or expression. In some instances, inhibitor of hyaluronan activity or expression comprises a small molecule inhibitor of CD44 activity or expression.

[0023] In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises an agonist of hyaluronidase activity or expression. In such ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises exogenous hyaluronidase, or the inhibitor of hyaluronan activity or expression comprises recombinant hyaluronidase, or the inhibitor of hyaluronan activity or expression comprises Pegvorhyaluronidase alfa (PVHA).

[0024] In some ~~embodiment~~examples, the therapeutically effective amount of the PVHA is between 0.01 to 0.5 mg/kg, or the therapeutically effective amount of the PVHA is between 0.02 to 0.4 mg/kg. In some ~~embodiment~~examples, the Pegvorhyaluronidase alfa (PVHA) is administered to the subject as a monotherapy. In some ~~embodiment~~examples, the therapeutically effective amount of the inhibitor of hyaluronan activity or expression is sufficient to reduce tumorigenesis at least 30% in the subject compared to an untreated individual. In such ~~embodiment~~examples, it is preferred that the tumorigenesis is quantified using by counting serrated polyps and carcinomas. In some ~~embodiment~~examples, the therapeutically effective amount of the inhibitor of hyaluronan activity or expression is sufficient to reduce tumor burden at least 20% in the subject compared to an untreated individual. In such ~~embodiment~~examples, it is preferred that the tumor burden is quantified using at least one of total number of tumors, average size of tumors, or tumor load. In some ~~embodiment~~examples, the therapeutically effective amount of the inhibitor of hyaluronan activity or expression is sufficient to reduce hyaluronan deposition in the tumor. In some ~~embodiment~~examples, the therapeutically effective amount of the inhibitor of hyaluronan activity or expression is sufficient to reduce collagen deposition in the tumor.

[0025] In some ~~embodiment~~examples, the biological sample comprises blood, blood plasma, sera, or tissue biopsy. In some ~~embodiment~~examples, the low levels of expression of PKCζ and PKCλ/ι comprises low transcription level, low translation level, or low activity level of PKCζ and PKCλ/ι.

[0026] ~~Aspect~~Examples disclosed herein provide methods of treating a serrated tumor in a subject by administering to the subject a therapeutically effective amount of an inhibitor of hyaluronan activity or expression. In one aspect, the present disclosure refers to use of a therapeutically effective amount of an inhibitor of hyaluronan activity or expression in the manufacture of a medicament for treating a serrated tumor in a subject. In some ~~embodiment~~examples, the inhibitor of hyaluronan activity or expression comprises Pegvorhyaluronidase alfa (PVHA). In some ~~embodiment~~examples, the Pegvorhyaluronidase alfa (PVHA) is administered to the subject as a monotherapy. In some ~~embodiment~~examples, the therapeutically effective amount of the PVHA is between 0.01 to 0.5 mg/kg. In some ~~embodiment~~examples, the therapeutically effective amount of the PVHA is between

0.02 to 0.4 mg/kg. In some ~~embodiment~~example**s**, the therapeutically effective amount of the inhibitor of hyaluronan activity or expression is sufficient to reduce tumorigenesis at least 30% in the subject compared to an untreated individual. In some ~~embodiment~~example**s**, a biological sample from the subject has a lower levels of expression of PKCζ and PKCλ/ι compared to levels of expression of PKCζ and PKCλ/ι in an individual without a serrated tumor.

[0027] In some ~~embodiment~~example**s**, the therapeutically effective amount of the inhibitor of hyaluronan activity or expression is sufficient to reduce tumorigenesis at least 30% in the subject compared to an untreated individual. In some cases, the tumorigenesis is quantified using by counting serrated polyps and carcinomas. In some ~~embodiment~~example**s**, the therapeutically effective amount of the inhibitor of hyaluronan activity or expression is sufficient to reduce tumor burden at least 20% in the subject compared to an untreated individual, which is optionally quantified using at least one of total number of tumors, average size of tumors, or tumor load. In some ~~embodiment~~example**s**, the therapeutically effective amount of the inhibitor of hyaluronan activity or expression is sufficient to reduce hyaluronan deposition in the tumor. In some ~~embodiment~~example**s**, the therapeutically effective amount of the inhibitor of hyaluronan activity or expression is sufficient to reduce collagen deposition in the tumor. In some ~~embodiment~~example**s**, the biological sample comprises blood, blood plasma, sera, or tissue biopsy.

BRIEF DESCRIPTION OF THE DRAWINGS

[0028] The patent application contains at least one drawing executed in color. Copies of this patent or patent application with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

[0029] Various aspects of the disclosure are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present disclosure will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the disclosure are utilized, and the accompanying drawings of which:

[0030] FIG.1, panels A-L exemplify simultaneous inactivation of PKCλ/ι and PKCζ drives serrated tumorigenesis in small intestine and colon. **Panel A** exemplifies cross images of wild-type (WT) and Pkci and Pkcz knockout (DKO^{IEC}). Arrows denote dilated intestine. **Panel B** exemplifies body weight of WT (n=15) and DKO^{IEC} mice (n-23). **Panel C** exemplifies Kaplan-Meier survival curve of WT (n=20) and DKO^{IEC} (n=22) mice. **Panel D** exemplifies hematoxylin and eosin (H&E) staining of small intestine and colon sections from