Supporting information

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Section I – Signaling network building and manual curation

1.1 Identification of pathways to include in the manually curated model

The AGS gastric adenocarcinoma cell line was chosen because AGS cells harbor mutations in numerous genes encoding proteins that are central in signaling pathways known to be affected in gastric adenocarcinomas: MAPK-, PI3K-, Wnt/β-catenin and NFκB-pathways [55,56,69–71]. These four signaling pathways were chosen as a focus for our signal transduction model. Mutations reported in AGS cells can be found in the databases listed in Table 1.

Table 1: Databases that report mutations in AGS cells.

| Database                                      | URL                                      | Reference |
|-----------------------------------------------|------------------------------------------|-----------|
| Cancer Cell Line Encyclopedia                  | http://www.broadinstitute.org/ccle/home  | [25]      |
| Catalogue of Somatic Mutations in Cancer (COSMIC) | http://cancer.sanger.ac.uk/cancergenome/projects/cosmic/ | [24,72]   |
| Genomics of Drug Sensitivity in Cancer         | http://www.cancerrxgene.org/             | [27]      |

1.2 Manual curation of the signal transduction model

1.2.1 Inclusion of signaling components

In order to construct a model depicting current knowledge on the MAPK, PI3K, Wnt/β-catenin and NF-κB pathways we used publicly available models in databases as guidance for inclusion of signaling components and interactions. Databases consulted are shown seen in Table 2.

Table 2: Databases consulted for guidance on manual curation.

| Database           | URL                                      | References |
|--------------------|------------------------------------------|------------|
| Biocarta           | http://www.biocarta.com/                | [73]       |
| NetPath            | http://www.netpath.org/                 | [74]       |
| PantherDB          | http://www.pantherdb.org/               | [75]       |
| Path2Models        | https://www.ebi.ac.uk/biomodels-main/path2models | [76]       |
| Pathway Commons    | http://www.pathwaycommons.org/          | [77]       |
| Pathway Interaction Database | http://pid.nci.nih.gov/ | [78]       |
| KEGG               | http://www.genome.jp/kegg/              | [79,80]    |
| Reactome           | http://www.reactome.org/                | [81–83]    |
| Science Signaling  | http://stke.sciencemag.org/cm/          |            |

All interactions included into the model were substantiated by references to literature documenting experimental evidence for the interaction. In addition, in depth literature review was used to enrich the model with experimentally documented details concerning modulating interactions with the chosen
signaling components and crosstalk between signaling pathways, as well as documented downstream interactions with pro- and anti-survival signaling modules. All literature references are given in Appendix A.

1.2.2 CellDesigner model
The collected pathway information was encoded in a CellDesigner SBML model [84,85] where edges are annotated with literature references from which the interactions are substantiated, see Figure 1. All proteins are annotated with the following information: Uniprot ID, gene name, presence at transcript level in AGS, and presence of mutations in AGS cells as reported in the databases listed in Table 1.

Figure 1: SBML model. Signaling network depicting signal transduction pathways related to growth of AGS gastric adenocarcinoma cells. Black arrows represent activating interactions, while red T arcs represent inhibitory interactions. Yellow boxes denote signal transduction components, and red boxes denote proteins whose gene harbor known mutations in AGS cells. Components identified by black circles mark the components targeted with specific inhibitors. The two diamond-shaped boxes “Prosurvival” and “Antisurvival” correspond to the two main readouts of the model. The curated model and its annotations are available in SBML format (S1 Dataset).

1.2.3 Exclusion of signaling components
The curated model was trimmed so that only nodes that are regulated by other nodes also present in the model were retained. Thus all model nodes are part of feedback loops, except for the two output nodes and some of their close upstream components (BAD, BAX, BCL2, Caspase3/7, Caspase8, Caspase9, CFLAR, CytochromeC and ITCH).

1.2.4 Final SBML signaling model
The final SBML signaling network consisted of 75 signaling components and two phenotypic output nodes, and 149 interactions, and the full SBML model with annotations can be found in S1 Dataset.
Section II – The Boolean model – definition

1.3 Boolean equations for the model of signal transduction in AGS cells

1.3.1 Default logical functions
We formulated a set of Boolean equations to formalize the evolution rules of each component. Boolean equations were formulated by the following general formula: A signaling component is active if any of its regulatory activators were active, while at the same time none of its regulatory inhibitors were active. For activators \( B, C \) and \( D \) and inhibitors \( E, F \) and \( G \) of the node \( A \), this translates to:

\[
A = (B \lor C \lor D) \land \neg (E \lor F \lor G)
\]

Note that several nodes only have activating regulators, and several nodes only have inhibitory regulators. As described in the main text a few exceptions to this rule were made. The logical formulae of all nodes can be found in S5 Table.

1.3.2 Exceptions to the default logical functions

1.3.2.1 Adjustments to comply with knowledge on protein activity regulation
The general Boolean equation stated above does not always comply with the biological understanding of protein activity regulation. Two Boolean rules were changed because of mechanistic knowledge on the protein activity regulation: 1) The equation describing the activation of the \( \beta \)-catenin destruction complex, which activates \( \beta \)-TrCP, resulting in degradation of \( \beta \)-catenin, and 2) the equation describing \( \beta \)-catenin activity.

For the \( \beta \)-catenin destruction complex to be active all subunits must be available, and so this multi-protein complex was said to depend on all three of Axin, GSK3 and CK1 (note that APC was excluded from the model as it wasn’t regulated by any component present in the model, and also note that Dvl was modelled as an intermediary between the Frizzled receptor and GSK3 [86], and not as part of the destruction complex). The logical function is:

\[
\beta TrCP = Axin \land GSK3 \land CK1
\]

instead of

\[
\beta TrCP = Axin \lor GSK3 \lor CK1
\]

The activity of \( \beta \)-catenin should further be governed by \( \beta \)-TrCP in a way so that the absence of \( \beta \)-TrCP causes \( \beta \)-catenin to be active. In the model IKKA is also positively regulating \( \beta \)-catenin activity, and the activity of \( \beta \)-catenin can, if IKKA is active, be sustained even when \( \beta \)-TrCP is active, since IKKA is phosphorylating and protecting \( \beta \)-catenin from destruction [64]. Thus, the equation describing activity of \( \beta \)-catenin was changed from the general formula:

\[
\beta \text{catenin} = IKKA \lor \neg \beta TrCP
\]

instead of

\[
\beta \text{catenin} = IKKA \land \neg \beta TrCP
\]
1.3.2.2 Adjustments to comply with reported observations on protein activity in AGS cells

Seven Boolean rules were adjusted to reflect observations on AGS steady state signaling as reported in publications:

TCF should be active in proliferating AGS cells [55,66], and thus the Boolean formula describing TCF activity was modified:

\[ TCF = \text{betacatenin or not } \text{NLK} \]

instead of

\[ TCF = \text{betacatenin and not } \text{NLK} \]

The logical functions describing the activity of SHC1, SOS, Raf, MEK and ERK were also redefined from the general parameterization by computing inhibitory regulators with OR NOT instead of AND NOT. The impact of negative feedback loops within the SOS/MEK/ERK pathway were thus reduced, replacing the cyclical attractor (in which ERK was cycling) by a single stable state in the model, hence matching published experimental observations for AGS cells, in which ERK is active [65,66]

Table 3: List of Boolean equations that were modified in the ERK pathway.

| General formula                                      | Modified                              |
|------------------------------------------------------|---------------------------------------|
| SHC1 = RTPK and not PTEN                             | SHC1 = RTPK or not PTEN               |
| SOS = GRB2 and not ERK                               | SOS = GRB2 or not ERK                 |
| MEK = (Raf or MAP3K) and not ERK                      | MEK = (Raf or MAP3K8) or not ERK      |
| ERK = MEK and not DUSP6                              | ERK = MEK or not DUSP6                |
| Raf = Ras and not (Rheb or AKT or ERK)               | Raf = Ras or not (Rheb or AKT or ERK) |
| TCF = betacatenin and not NLK                         | TCF = betacatenin or not NLK          |

Section III - The Boolean model – calibration and validation

1.4 Literature review for determination of model component activity state

The model protein activities were determined based on a literature review of experimental investigations of proliferating AGS cells. We identified a total of 219 experimental protein state observations relevant for our model reported in 72 unique papers (specified in Appendix B). Most observations were from Western blots, but we also included some reports based on PCR (polymerase chain reaction), EMSA (electrophoretic mobility shift assay), IP (immunoprecipitation), flow cytometry, LC-ES-IT (liquid chromatography electrospray/ionization trap), IHC (immunohistochemistry) or fluorescent reporter proteins. All observations are listed in S2 Table.

Literature reports of protein activity levels were found for 46 of 75 model signal transduction components. We reasoned that whenever the information from several scientific publications consistently implied that a specific protein should be active or inactive in proliferating AGS cells (for example AKT was consistently found to be active), the observed stable state attractor should reflect this (the component AKT value should equal 1). For 21 of the 46 components several, independent and consistent reports were found, and
these activity state values were used for guiding and validating the Boolean equations. Of the 25 component observations that were less well substantiated, ten were found to be in conflict with the predicted state in the attractor. We consider compliance with the 21 well documented components to be of highest importance and therefore concluded that the stable state of the model adequately matches experimental observations of protein activities in actively growing AGS cells.

In searching PubMed for relevant articles, we initially searched for all AGS cell papers reporting Western blots published after the year 2000. This search resulted in 376 papers (the literature survey was performed in June-September 2013). For model proteins with none or only few observations in these initially retrieved papers, a second round of PubMed searches was done retrieving all papers that could be found with the keywords “AGS [missing protein]”. This search was not restricted by the time of publication. In addition, Google was used to search for papers with keywords “AGS [missing protein]”, identifying a few articles that were not returned by PubMed’s internal search engine (even though the paper was indexed by PubMed).

For all observations their suitability was assessed according to the quality of the reported Western blots (subjective perception), specifications of whether cells were in complete medium or starved, whether phosphorylation events or only total protein levels were reported, and if the observation agreed with observations in other papers. An assessment of whether a protein was active or not was then done and activity levels were dichotomized into the two states ON or OFF. See S2 Table.

1.5 Literature review of AGS signal transduction perturbation

As an additional test of the validity of the model, the asymptotic behavior of the perturbed model was verified by comparing it with the behavior observed in experimental perturbations. We retrieved information from 56 published experiments where specific signaling proteins had been activated or inhibited (S6 Table), and recorded the reported effects of these perturbations on signaling proteins. The experimentally observed effects were then compared with the effects found for the corresponding nodes in model simulated perturbations. The model accurately reproduced 21 published observations. None of the 56 observations were contradicted, meaning that the model never proposed the result opposite to findings in published reports. For 35 observations, the reported change in activity was not captured by the logical model. We consider this to be related to the likelihood that not all activity changes observable on a continuous scale by methods like Western blot will translate into a qualitative signaling change.

In order to capture signal transduction dynamics, the literature was surveyed for reports on AGS cell perturbation experiments where the target was a node in our curated model, and the observed perturbation effect pertained to another node in our model. The papers retrieved from the following PubMed-searches, “AGS siRNA” (163 papers), “AGS [relevant specific inhibitor]”, and “AGS inhibitor”, were assessed according to the criteria specified above and resulted in 56 observations spanning 20 unique publications that were of relevance to the model (see appendix C).

1.6 Model validation

The predicted stable state of the model fit data from literature, as seen in Table 4. This list of 21 components is a summary of the observations shown in S2 Table, with only the observations of highest confidence included.
Table 4: Model fit with literature data. In the left column the most convincing consensus observations are shown, and contrasted with the model stable state in the right lane.

| Protein  | Literature | Model |
|----------|------------|-------|
| AKT      | On         | 1     |
| Bax      | Off        | 0     |
| BCL2     | On         | 1     |
| β-catenin| On         | 1     |
| Caspase3/7| Off       | 0     |
| Caspase8 | Off        | 0     |
| CCND1    | On         | 1     |
| cMYC     | On         | 1     |
| ERK1/2   | On         | 1     |
| GSK3     | Off        | 0     |
| JNK1/2   | Off        | 0     |
| MMP      | On         | 1     |
| NFkB     | On         | 1     |
| p38      | Off        | 0     |
| p53      | Off        | 0     |
| PI3K     | On         | 1     |
| PTEN     | Off        | 0     |
| Rac      | On         | 1     |
| Ras      | On         | 1     |
| S6K      | On         | 1     |
| TCF      | On         | 1     |

An extended table, where all literature reports are contrasted with model predictions, can be seen in S3 Table. In S3 Table strongly colored components (red/green) are substantiated by several independent and consistent literature observations, and are the same components as listed in Table 4. Less strongly colored components (light red/green) in S3 Table are reported in few papers or with inconsistently reported observations among papers. Yellow colored components have been reported to show both an ON and an OFF state within the same experiment, and for grey colored components there are no published experiments available. Most literature derived observations are coherent with the model, albeit with some exceptions for a few of the less confident literature observations, but as the quality and/or consistency across independent reports for these observations was substantially lower than the observations in Table 4 these discrepancies were not analyzed further.
Section IV – Model reduction and dual interaction from p38alpha to Antisurvival

1.7 Model reduction
Using the built-in model reduction tool of GINsim a logical model can be reduced to a model consisting of fewer nodes, while stable states of the original logical model are preserved. During model reduction, all logical equations are replaced by logical parameters, which amounts to having the logical rules in a lengthy normal disjunctive form. These are provided in S7 Table for the reduced logical model depicted in Figure 3 in the manuscript, along with the reduced model in S3 Dataset. S7 Table was not used for drug synergy analysis, but can provide details to the interactions in model. Compressed expressions of the logical parameters are provided in S8 Table. For each interaction S7 Table specifies the context determining if the interaction is positive, neutral or negative. The context is a discrete vector containing the activity values of all nodes contributing to the nature of the interaction. We use it here to describe the context-dependent nature of the dual interaction from p38alpha to Antisurvival.

1.8 Dual interaction from p38alpha to Antisurvival
After model reduction the interaction from node ‘p38alpha’ to ‘Antisurvival’ is shown as ‘dual’ (Figure 3, Manuscript and S7 Table), where p38alpha can increase the value of ‘Antisurvival’ in some contexts, and decrease it in other contexts. See S7 Table for a full list of contexts that affects the interaction from p38alpha to Antisurvival. From S7 Table it can be seen that two scenarios can hypothetically happen:

(1) p38alpha inhibition can decrease Antisurvival if AKT is inactive

(2) p38alpha inhibition can increase Antisurvival if AKT is active

Scenario (1) is never observed in our simulations. For (1) to happen one of the drugs in a drug combination would have to cause p38alpha to be activated as p38alpha is inactive in the unperturbed case, and AKT to become inactivated (AKT is active in the unperturbed case). Then if p38alpha inhibition is the second drug in the drug pair we could observe behavior (1). However, among the drug inhibitions we simulated no single drug has the ability to both activate p38alpha and inactivate AKT, and therefore (1) is never observed.

Section V – Simulations of FOXO knockout
From model simulations it was hypothesized that FOXO is important to the predicted and validated synergies. Model simulations where FOXO was forced to be inactive (i.e. knock-out simulations) showed that the synergies of TAK1 and PI3K, and AKT and MEK, and MEK and PI3K were all dependent on FOXO, while the synergy of AKT and MEK was only partially dependent on FOXO (the synergy was weakened but not abolished when FOXO knock-out was simulated). The results from simulations can be seen in Table 5.
Table 5: Simulations of FOXO knock-out reveals that FOXO is necessary to explain the predicted synergies. Node A and B denote nodes simulated to be inhibited. FOXO indicates whether a FOXO knock-out experiment was simulated (OFF). Prosurvival and Antisurvival show the values of the two phenotypic outputs, which ranges from 0 to 3 for both, and Growth denotes the difference between Prosurvival and Antisurvival, which thus ranges from -3 to 3. In the Synergy column it can be seen that upon FOXO knock-out the synergies of TAK1-PI3K, MEK-PI3K and AKT-TAK1 were abolished, while the synergy of AKT-MEK was still present (albeit weakened). The last column recapitulates the experimental observations of synergies.

| Node A    | Node B    | FOXO | Prosurvival | Antisurvival | Growth | Model | Experiment |
|-----------|-----------|------|-------------|--------------|--------|-------|------------|
| TAK1      | PI3K      |      | 2           | 2            | 0      | 1     | Yes        |
| TAK1      | PI3K      | OFF  | 2           | 1            | 1      | 0     | Yes        |
| MEK       | PI3K      |      | 2           | 1.5          | 0.5    | 0.5   | Yes        |
| MEK       | PI3K      | OFF  | 2           | 1            | 1      | 0     | Yes        |
| AKT       | MEK       |      | 2.5         | 2            | 0.5    | 1     | Yes        |
| AKT       | MEK       | OFF  | 2.5         | 1.5          | 1      | 0.5   |            |
| AKT       | TAK1      |      | 3           | 2            | 1      | 1     | Yes        |
| AKT       | TAK1      | OFF  | 3           | 1            | 2      | 0     |            |
| MEK       | p38alpha  |      | 2           | 1            | 1      | 0.5   | No         |
| MEK       | p38alpha  | OFF  | 2           | 1            | 1      | 0.5   |            |
| PI3K      |           |      | 2           | 1            | 1      | -     |            |
| PI3K      |           | OFF  | 2           | 1            | 1      | -     |            |
| MEK       |           |      | 2           | 0.5          | 1.5    | -     |            |
| MEK       |           | OFF  | 2           | 0.5          | 1.5    | -     |            |
| AKT       |           |      | 3           | 1            | 2      | -     |            |
| AKT       |           | OFF  | 3           | 1            | 2      | -     |            |
| p38alpha  |           |      | 3           | 0            | 3      | -     |            |
| p38alpha  |           | OFF  | 3           | 0            | 3      | -     |            |
| TAK1      |           |      | 3           | 0            | 3      | -     |            |
| TAK1      |           | OFF  | 3           | 0            | 3      | -     |            |
| Unperturbed|           |      | 3           | 0            | 3      | -     |            |

In addition to the importance of FOXO activation, we found AGS cell growth to be highly dependent on β-catenin, since administration of the β-catenin inhibitor PKF118-310 even at low concentrations profoundly impeded cell growth in comparison with its effect reported for other cell lines [87–89]. Our AGS logical model simulations correlate well with these experimental observations since the growth output exhibited high dependence on the state of the node representing β-catenin, yet model simulations predicted that this trait was not dependent on β-catenin induced activation of FOXO. We thus searched for inhibitor combinations targeting β-catenin and any other node accounted for by the model, to suggest new potent drug combinations. While we found that none of the pairwise inhibitions of components included in the model were able to inactivate β-catenin and simultaneously activate FOXO, model simulations revealed that the strong anti-proliferative state induced by β-catenin inhibition could be further strengthened by simulating activation of FOXO (output values: Prosurvival = 0, Antisurvival = 2,
contrasted with $Prosurvival = 0$, $Antisurvival = 1$ for $\beta$-catenin inhibition alone), emphasizing the central position of FOXO regulation in AGS growth.

Section VI – Cell growth experiments

1.9 Chemical inhibitors

Seven chemical inhibitors were chosen for cell growth experiments. Criteria that guided the selection of inhibitors include:

- Chemical properties similar to clinically approved drugs (Lipinski’s rule of five)
- Well characterized in in-vitro kinase screens, in order to know of any off-target effects, and preferentially choose inhibitors with few off-target effects, following the recommendation by the MRC lab whenever possible (http://www.ppu.mrc.ac.uk/). The inhibitors used for perturbation experiments are shown in Table 6.

Table 6: Chemical inhibitors used in perturbation experiments.

| Inhibitor             | Target | Predicted state of target in unperturbed model | Dose  |
|-----------------------|--------|-----------------------------------------------|-------|
| (5Z)-7-oxozaenol      | TAK1   | ON                                           | 0.5 µM|
| AKTi-1,2              | AKT    | ON                                           | 10 µM |
| BIRB0796              | p38    | OFF                                          | 5 µM  |
| CT99021               | GSK3   | OFF                                          | 5 µM  |
| PD0325901             | MEK1/2 | ON                                           | 35 nM |
| PI103                 | PI3K   | ON                                           | 0.7 µM|
| PKF118-310            | $\beta$-catenin | ON                       | 150 nM|

1.9.1.1 Determination of GI50 concentrations

For each drug a dose-response profile was initially determined, in order to find a dose that inhibited growth by 50%, and which was the dose used in combination experiments. If there was no knowledge on the effective concentration range to be used a 10x dilution series was performed initially, before a 2x dilution series could be done. If the GI50 or a proxy could be found in public databases (Genomics of Drug Sensitivity in Cancer) or deduced from literature (either for AGS cells or other cells) the dilution series would start with a 5x or 2x dilution series.

1.9.1.1.1 Cell growth experiments

All growth measurements were performed in real time, where the xCELLigence RTCA SP/DP (Roche) instrument was used to estimate growth. Real-time measurements of the impedance across the gold arrays at the bottom of wells in a well-plate are reported in the dimensionless unit of cell index which is taken to correspond to cell proliferation.
1.9.1.1.2 Single inhibitors

Figure 2-15 shows the dose response profiles for the seven inhibitors included in the study. In the left lane of figures dose response growth curves versus time for each inhibitor can be seen, and in the right lane of figures the corresponding dose-response profile 48 hours after adding inhibitors is shown. Both the dose-response profile and the dose-response growth curves formed a basis for determining a dose to be used in combination experiments, which should be close to the GI50. DMSO controls were conducted with concentrations matching the highest concentrations used in experiments. In the following paragraphs our results for single inhibitors are compared to literature-derived data.
Figure 2: PI103 dose-response. Red: Control. Green: 30 nM. Blue: 150 nM. Pink: 750 nM. Cyan: 3750 nM. Purple: 18.75 µM.

Figure 3: PI103 dose-response. Estimated GI50 is 0.683 µM.

Figure 4: PKF118-310 dose-response. Beige: Control. Red: 44 nM. Pink: 67 nM. Green: 100 nM. Cyan: 150 nM. Blue: 225 nM. Purple: 337.5 nM.

Figure 5: PKF118-310 dose-response. Estimated GI50 is 148 nM.

Figure 6: PD0325901 dose-response. Beige: Control. Red: 0.8 nM. Green: 4 nM. Blue: 20 nM. Pink: 100 nM. Cyan: 500 nM. Purple: 2500 nM.

Figure 7: PD0325901 dose-response. Estimated GI50 is 31 nM.
Figure 8: (5Z)-7-oxozeaenol dose response. Beige: Control. Red: 125 nM. Pink: 250 nM. Green: 500 nM. Cyan: 1 µM. Purple: 2 µM.

Figure 9: (5Z)-7-oxozeaenol dose response. Estimated GI50 is 0.55 µM.

Figure 10: AKTi-1,2 dose-response. Cyan: control. Purple: 2 µM. Beige: 4 µM. Green: 8 µM. Dark green: 12 µM. Blue: 16 µM. Red: 32 µM.

Figure 11: AKTi-1,2 dose response. Estimated GI50 is 10.0 µM. Note that the 8 µM wells in Figure 10 were removed for the estimation on GI50.

Figure 12: CT99021 dose response. Pink: control. Red: 0.5 µM. Green: 5 µM. Blue: 50 µM.

Figure 13: CT99021 dose response. Estimated GI50 is 15.3 µM.
1.9.1.2 Observed GI50 values for inhibitors acting on AGS cells

1.9.1.2.1 PI3K inhibitor
The PI3K inhibitor PI103 was found to have a GI50 of 0.7 µM for AGS cells, which fit data from the literature, where the GI50 of PI103 for AGS cells has been reported to be 0.76 µM[90].

1.9.1.2.2 β-catennin inhibitor
The β-catennin inhibitor PKF118-310 was highly potent in AGS cells, and proved to be very difficult to work with in experiments, as there was either an all-or-nothing response for a given concentration. 150 nM was used as an estimate of the GI50, even though this would typically give a full effect. (At 100 nM there would typically be seen no effect). In other cells the GI50 value has been found in the range 0.31-3.48 µM[87–89], indicating that AGS cells are indeed very sensitive to this inhibitor.

1.9.1.2.3 MEK inhibitor
The MEK inhibitor PD0325901 was found to have a GI50 of roughly 35 nM. This fits data from the Genomics of Drug Sensitivity in Cancer database, where the GI50 for AGS cells has been found to be 0.013-0.032 µM.

1.9.1.2.4 TAK1 inhibitor
The TAK1 inhibitor (5Z)-7-oxozeaenol was found to have a GI50 of 0.5 µM in AGS cells. In literature the GI50 for other cell lines has been reported in the range 0.02-60 µM [91,92]. In KRAS-dependent colon cancer cell lines concentrations in the range 0.625-1.25 µM of (5Z)-7-oxozeaenol has been found to promote apoptosis[92], and in another work AGS cells have been described as KRAS dependent[65], and the GI50 found in our experiments are thus in agreement with the few reports of the effects of (5Z)-7-oxozeaenol on proliferation in cell line experiments.

1.9.1.2.5 AKT inhibitor
The AKT inhibitor AKTi-1,2 (AKT inhibitor VIII) was found to have a GI50 in AGS cells of 10 µM. This fits data from the Genomics of Drug Sensitivity in Cancer database, where the GI50 for AGS cells is estimated to be 7.6 µM.
1.9.1.2.6 GSK3 and p38alpha inhibitors
For the two inhibitors CT99021 and BIRB0796 calculated GI50 values are included for reference. This GI50 value is however probably not biologically meaningful as the concentration of each inhibitors is very high compared to concentrations that are typically used to inhibit their intended target. This also coincides with data from the Genomics of Drug Sensitivity in Cancer database, where the GI50 for these inhibitors is estimated by extrapolation to be > 200 µM for AGS cells.

1.9.1.2.7 GI50 vs time
The GI50 varied with time, and so an initial experiment was performed to find a time point at which the GI50 could be estimated. The GI50 stabilized for all inhibitors and combinations of inhibitors within 48 hours after addition of inhibitors, and so this was chosen as the time point for further analysis (both single drug dose response curves, and for drug combination experiments). All growth curves were still recorded in real time, and the 48h time point was used for calculating GI50s and combinatorial indexes (see below). Figure 16 and Figure 17 show two examples of GI50 estimates versus time.

![Figure 16: GI50 for PI103 vs time (48h-96h).](image)

![Figure 17: GI50 for PD0325901 vs time (48h-96h) ](image)

1.10 Synergy assessment

1.10.1 Experimental determination of GI50
In cell growth experiments the Loewe additivity definition of synergy was used [28]. Initially, a dose-response experiment of each inhibitor was performed to find a concentration of each inhibitor that inhibited growth of cells by half compared to the control (no inhibitor). This dose of the drug is the GI50 (growth inhibition 50%), and for combination experiments a dose close to but less than the GI50 was sought. Since the exact effect of all drugs will vary slightly between biological replicates, experiments
were set up so that both single drugs and their combinations would be tested within one experiment, i.e.
within the same biological replicate.

1.10.1.1 Experimental design
All single drugs were tested in three doses within one experiment, in a 2-fold dilution series from the GI50
dose. Similarly the combinations were tested in three doses within one experiment. The highest dose was
obtained by mixing the two inhibitors with equal volumes from the GI50 concentration solutions, and thus
the concentration of each inhibitor in the combination was half of the GI50. Then a 2-fold dilution series
was made so that the doses of each inhibitor were a quarter and an eight of their GI50 doses, which would
give three doses where synergy could be assessed according to the Loewe definition. Note that the highest
dose of inhibitors in a combination were created from the same aliquots as the single inhibitors, thus
ensuring that the concentration in a combination was halved, even if the exact concentration of the single
inhibitor deviated slightly from the GI50 concentration.

1.10.1.2 Combination indexes
A combination index (CI) was also calculated for all combinatorial experiments based on the analysis of
Chou and Talalay [29], where the CompuSyn software was used for calculating the CI values [68]. The
combinatorial index is based on a mechanistic approach to synergy assessment. A median-effect plot is
made from specific dose-response data, where the potency and shape of the dose-response is determined,
and thus the entire dose-effect curve is predicted. This analysis also takes into account the steepness of the
dose-response curves when the effect of combining halves is analyzed (http://www.combosyn.com/)
[68,93]. For analyzing the combination index the effect on growth 48 hours after adding inhibitors were
used. The GI50 was found to vary with time, but had reached a stable level at this time, as described in the
paragraph “GI50 vs time”. Note that a CI value can only be reliably computed if a dose-response
relationship to an inhibitor can be found, which made CI value calculations impossible for drugs that
target proteins that are inactive in proliferating AGS cells (CT99021 targeting GSK3 and BIRB0796
targeting p38).

1.10.1.2.1 Drug combinations
Figures 18-38 shows one representative biological replicate for all 21 drug combinations of the seven
inhibitors: (5Z)-7-oxozeaenol; AKTi-1,2; BIRB0796; CT99021; PD0325901; PI103 and PKF118-310.
Figure 18 to Figure 21 show the four synergies found. For all figures the combination of two drugs has
half the concentration of each single drug in the combination. If the effect of a combination is more
profound than the best-performing single inhibitor the effect is synergistic. The plots show the reported
Cell Index, which is proportional to the number of cells, on the y-axis, and the time in hours on the x-axis.
The synergy of inhibiting both PI3K and MEK supports previously published observations, including
findings in a murine hematopoietic cell line [30], a breast cancer cell line [31], xenograft models of
colorectal carcinomas [33], and colon cancer cell lines [6]. Cancer treatment based on combined inhibition
of PI3K and MEK is currently being pursued in several phase 1 clinical trials for advanced solid cancer
(including pancreatic, breast, non-small cell lung cancer and colorectal cancer; see for instance clinical
trials NCT01347866, NCT01363232, NCT01337765 and NCT00996892).

Similarly, the synergistic effect of combining MEK and AKT inhibitors has been previously shown
effective against a panel of lung cancer cell lines [32], as well as against thyroid cancer cell lines [34], and
is investigated in several clinical trials (including multiple myeloma, breast, endometrial, colorectal, non-
small cell lung cancer, pancreatic cancer, ovarian cancer; see for instance clinical trials NCT01476137, NCT01138085, NCT01907815 and NCT01333475).
Figure 18: MEK1/2 (PD0325901) and PI3K (PI103) inhibition. PD0325901 35 nM (green) and PI103 0.7 µM (blue) vs their combined effect (pink) and control (red). The combination is synergistic.

Figure 19: MEK1/2 (PD0325901) and AKT (AKTi-1,2) inhibition. PD0325901 35 nM (blue) and AKTi-1,2 10 µM (green) vs their combined effect (pink) and control (red). The combination is synergistic.

Figure 20: AKT (AKTi-1,2) and TAK1 ((5Z)-7-oxozeaenol) inhibition. AKTi-1,2 10 µM (green) and (5Z)-7-oxozeaenol 0.5 µM (blue) vs their combined effect (pink) and control (red). The combination is synergistic.

Figure 21: PI3K (PI103) and TAK1 ((5Z)-7-oxozeaenol) inhibition. PI103 0.7 µM (green) and (5Z)-7-oxozeaenol (blue) vs their combined effect (pink) and control (red). The combination is synergistic.

Figure 22: AKT (AKTi-1,2) and PI3K (PI103) inhibition. AKTi-1,2 10 µM (blue) and PI103 0.7 µM (green) vs their combined effect (pink) and control (red). The combination is non-synergistic.

Figure 23: AKT (AKTi-1,2) and p38 alpha (BIRB0796) inhibition. AKTi-1,2 10 µM (blue) and BIRB0796 5 µM (green) vs their combination (pink) and control (red). The combination is non-synergistic.
Figure 24: AKT (AKTi-1,2) and GSK3 (CT99021) inhibition. AKTi-1,2 10 µM (green) and CT99021 5 µM (blue) vs their combination (pink) and control (red). The combination is non-synergistic.

Figure 25: AKT (AKTi-1,2) and β-catenin (PKF118-310) inhibition. AKTi-1,2 10 µM (green) and PKF118-310 150 nM (blue) vs their combination (pink) and control (red). The combination is non-synergistic.

Figure 26: MEK1/2 (PD0325901) and TAK1 ((5Z)-7-oxozeaenol) inhibition. PD0325901 35 nM (blue) and (5Z)-7-oxozeaenol 0.5 µM (green) vs their combination (pink) and control (red). The combination is non-synergistic.

Figure 27: MEK1/2 (PD0325901) and β-catenin (PKF118-310) inhibition. PD0325901 35 nM (green), PKF118-310 150 nM (blue) vs their combination (pink) and control (red). The combination is non-synergistic.

Figure 28: MEK1/2 (PD0325901) and GSK3 (CT99021) inhibition. PD0325901 35 nM (green) and CT99021 5 µM (blue) vs their combination (pink) and control (red). The combination is non-synergistic.

Figure 29: MEK1/2 (PD0325901) and p38 alpha (BIRB0796) inhibition. PD0325901 35 nM (blue) and BIRB0796 5 µM (green) vs their combination (pink) and control (red). The combination is non-synergistic.
Figure 30: PI3K (PI103) and β-catenin (PKF118-310) inhibition. PI103 0.7 µM (green) and PKF118-310 150 nM (blue) vs their combination (pink) and control (red). The combination is non-synergistic.

Figure 31: PI3K (PI103) and GSK3 (CT99021) inhibition. PI103 0.7 µM (blue) and CT99021 5 µM (green) vs their combination (pink) and control (red). The combination is non-synergistic.

Figure 32: PI3K (PI103) and p38 alpha (BIRB0796) inhibition. PI103 0.7 µM (blue) and BIRB0796 5 µM (green) vs their combination (pink) and control (red). The combination is non-synergistic.

Figure 33: GSK3 (CT99021) and β-catenin (PKF118-310) inhibition. CT99021 5 µM (green) and PKF118-310 150 nM (blue) vs their combination (pink) and control (red).

Figure 34: GSK3 (CT99021) and p38 alpha (BIRB0796) inhibition. CT99021 5 µM (blue) and BIRB0796 5 µM (green) vs their combination (pink) and control (red). The combination is non-synergistic.

Figure 35: TAK1 ((5Z)-7-oxozeaenol) and β-catenin (PKF118-310) inhibition. (5Z)-7-oxozeaenol 0.5 µM (blue) and PKF118-310 150 nM (green) vs their combination (pink) and control (red). The combination is non-synergistic.
Figure 36: TAK1 ((5Z)-7-oxozeaenol) and GSK3 (CT99021) inhibition. (5Z)-7-oxozeaenol 0.5 µM (blue) and CT99021 5 µM (green) vs their combination (pink) and control (red). The combination is non-synergistic.

Figure 37: TAK1 ((5Z)-7-oxozeaenol) and p38 alpha (BIRB0796) inhibition. (5Z)-7-oxozeaenol 0.5 µM (blue) and BIRB0796 5 µM (green) vs their combination (pink) and control (red). The combination is non-synergistic.

Figure 38: β-catenin (PKF118-310) and p38 alpha (BIRB0796) inhibition. PKF118-310 150 nM (blue) and BIRB0796 5 µM (green) vs their combination (pink) and control (red). The combination is non-synergistic.
Appendix A
Literature references for the curated network model of MAPK-, PI3K, Wnt/β-catenin and NF-κB pathways and their crosstalk (for full reference details, see Supplementary references next page):
[37,38,62,64,86,94–158].

Appendix B
The 218 observations of the state of proteins in AGS cells reported in 71 unique papers (for full reference details, see Supplementary references next page):
[65,66,90,110,146,159–223].

Appendix C
Literature references for the AGS signal transduction perturbation experiments (for full reference details, see Supplementary references next page):
[66,90,159,162,164,166,172,176,178,183,185,189,194,195,197,205,219,224,225].
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