models for both the $GABA_A$ receptor and 11β-hydroxylase when performing their docking studies. Nevertheless, they were still able to successfully identify compounds that were potent $GABA_A$ receptor modulators but lacked significant 11β-hydroxylase inhibitory activity.

Recently, Laverty *et al.* reported the structure of a synaptic $GABA_A$ receptor using cryo-electron microscopy [10]. Thus, one could reasonably expect that *in silico* screening assays utilizing this new structure could provide even more accurate predictions of $GABA_A$ receptor modulatory potency and anesthetic activity.

In summary, there is a compelling need for new general anesthetics that are devoid of the side effects that risk harm to patients. The work by Cayla and colleagues provides proof-of-concept for the use of *in silico* docking approaches to rapidly screen virtual libraries to identify compounds with potent anesthetic activities that are devoid of side effects mediated by off-target sites. We look forward to the day when a novel anesthetic agent first identified by such approaches is available for use in patients.

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References

1. Hemmings, H.C., Jr. *et al.* (2019) Towards a comprehensive understanding of anesthetic mechanisms ofaction: a decade of discovery. *Trends Pharmacol. Sci.* 40, 464–481
2. Cayla, N.S. *et al.* (2019) A newly developed anesthetic based on a unique chemical core. *Proc. Natl. Acad. Sci. U. S. A.* 116, 15706–15715
3. Mascia, M.P. *et al.* (2005) Ethyl 2-(4-bromophenyl)-1-(2,4-dichlorophenyl)-1H-4-imidazolecarboxylate is a novel positive modulator of GABAA receptors. *Eur. J. Pharmacol.* 516, 204–211
4. Wagner, R.L. and White, P.F. (1984) Etomidate inhibits adrenocortical function in surgical patients. *Anesthesiology* 61, 647–651
5. Shanmugasundararaj, S. *et al.* (2013) Carboetomidate: an analog of etomidate that interacts weakly with 11beta-hydroxylase. *Anesth. Analg.* 116, 1249–1256
6. Cotten, J.F. *et al.* (2010) Carboetomidate: a pyrrole analog of etomidate designed not to suppress adrenocortical function. *Anesthesiology* 112, 637–644
7. Akhtar, S. (2018) Pharmacological considerations in the elderly. *Curr. Opin. Anaesthesiol.* 31, 11–18
8. McKinstry-Wu, A.R. *et al.* (2015) Discovery of a novel general anesthetic chemotype using high-throughput screening. *Anesthesiology* 122, 325–333
9. Yang, X. *et al.* (2018) High-throughput screening in larval zebrafish identifies novel potent sedative-hypnotics. *Anesthesiology* 129, 459–476
10. Laverty, D. *et al.* (2019) Cryo-EM structure of the human α1β3γ2 $GABA_A$ receptor in a lipid bilayer. *Nature* 565, 516–520

Forum

You Cannot Have Your Synergy and Efficacy Too

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Synergistic drugs are preferred in combination therapies for many diseases, including viral infections and cancers. Maximizing synergy, however, may come at the cost of efficacy. This synergy–efficacy trade-off appears to be widely prevalent and independent of the specific drug interactions yielding synergy. We present examples of the trade-off in drug combinations used in hepatitis C, HIV, and cancer therapies and believe that screens for optimal drug combinations that presently seek to maximize synergy may be improved by considering the trade-off.

Synergistic Drug Combinations

Drug combinations form the mainstay of current therapies for cancers, infectious diseases, and lifestyle disorders [1]. They have two significant advantages over therapies involving single drugs [1]: first, by attacking multiple targets, they may reduce the chances of drug resistance; and, second, because the drugs can each be used at lower dosages in combination than if used alone, they may cause less severe side-effects. Here, drugs that exhibit synergistic interactions are particularly beneficial. Broadly, synergistic interactions result in the drug combination having an effect that is larger than the independent effects of the individual drugs combined [1–3]. Consequently, synergistic drug combinations can achieve the desired efficacies at much lower dosages, further reducing side-effects and costs. Alternatively, they may allow greater efficacies at tolerable toxicities [4]. Significant efforts are invested therefore in identifying synergistic drug combinations. For example, every pair of 19 anti-HIV drugs [5] and numerous two- and three-drug combinations for hepatitis C virus (HCV) infection [6] have been assessed to identify the most synergistic combinations. Recognizing the wider importance of such screening, algorithms and automated platforms, including those using modern deep learning techniques, have been proposed for the identification of synergistic drug combinations [3,7,8].

Sounding a cautionary note, we argue here that this quest for synergy, while desirable, cannot be unconstrained. Beyond a limit, synergy may come at the cost of efficacy. Evidence of this trade-off between synergy and efficacy

Table 1. Drug Combinations Exhibiting the Synergy–Efficacy Trade-Off

Disease	Drug combination	Observation of trade-off			Refs	Summary
HCV infection	Interferon + ribavirin	Efficacy (cure rate, %)	62	76	[9]	Increase in cure rate (synergy) decreases with interferon efficacy
		Bliss synergy (β_B)	42	31		
		Efficacy (ε)[a]	0.5	0.9	[10]	Synergy decreases with efficacy
	Boceprevir + erlotinib	*CI*	0.25	0.75		
	Simeprevir + dasatinib		0.45	0.65		
	Boceprevir + dasatinib		0.25	0.55		
	Telaprevir + erlotinib		0.2	0.5		
	Telaprevir + dasatinib		0.4	0.6		
	Daclatasvir + dasatinib		0.4	0.7		
	Sofosbuvir + dasatanib		0.25	0.6		
	Anti-CLDN1 + erlotinib		0.25	0.65		
	Anti-CD81 + erlotinib		0.3	0.7		
	Anti-CLDN1 + boceprevir		0.05	0.5		
HIV infection	Nevirapine + zidovudine	Efficacy (ε)	0.62	0.999	[5]	Synergy decreases with efficacy
		Bliss synergy (β_B)	0.048	0.003		
	Dolutegravir + tenofovir	Efficacy (ε)	0.8	0.997	[11]	
		Bliss synergy (β_B)	0.12	0.002		
Cancer	WEHI-539 (fixed concentration) + cisplatin	Cell line	SW1353		[13]	Synergy decreases with cisplatin concentration (efficacy)
		Cisplatin (μM)	12.5	100		
		Bliss synergy (β_B)	>0.12	~0		
		Cell line	CH2879			
		Cisplatin (μM)	0.78	100		
		Bliss synergy (β_B)	~0.3	~0		
		Cell line	L835			
		Cisplatin (μM)	6.25	100		
		Bliss synergy (β_B)	~0.2	~0.05		
		Cell line	L3252			
		Cisplatin (μM)	3.13	100		
		Bliss synergy (β_B)	~0.5	~0		
	Ruxolitinib + panobinostat	Efficacy (ε)	0.89	0.96	[14]	Synergy decreases with efficacy
		Bliss synergy (β_B)	0.14	0.08		
	Ruxolitinib + withaferin A	Efficacy (ε)	0.32	0.47		
		Bliss synergy (β_B)	0.22	0.12		

[a]Defined as the fraction of infection events prevented by the drug(s).

is widespread, although it has not been commensurately recognized.

Examples of the Synergy–Efficacy Trade-Off

We trace the earliest evidence of the synergy–efficacy trade-off to studies nearly 15 years ago on the combination of interferon and ribavirin (Table 1), which was then the standard of care for chronic HCV infection [9]. Ribavirin alone was found not to cure HCV infection. Interferon monotherapy yielded cure rates of ~20% [9]. Combining interferon with ribavirin improved cure rates dramatically to ~62% on average [9]. The drugs thus acted synergistically. The extent of synergy, however, was reduced when interferon was more potent and resulted in higher cure rates by itself. The pegylated form of interferon, for instance, elicited cure rates of ~45% alone, compared

with ~20% by its nonpegylated form, indicating greater interferon efficacy in the pegylated form [9]. Combining ribavirin with pegylated interferon increased the cure rate to ~76%, a much smaller increase than above, implying reduced synergy with increased efficacy [9], indicative of the synergy–efficacy trade-off.

Formally, let ε_1 and ε_2 be the efficacies of drug 1 and drug 2, respectively, and let ε_{comb} be their combined efficacy. If the drugs were to act independently, ε_{comb} would be equal to ε_B given by the Bliss independence formula: $\varepsilon_B = 1 - (1 - \varepsilon_1)(1 - \varepsilon_2)$ [2]. When ε_{comb} is higher than ε_B, the combination exhibits Bliss synergy, quantified as $\beta_B = \varepsilon_{comb} - \varepsilon_B$ (Box 1). Thus, higher β_B implies higher synergy. If we define efficacy as cure rate, it follows that β_B decreases as ε_{comb} increases (Table 1), quantifying the synergy–efficacy trade-off in the interferon–ribavirin combination discussed above.

Chronic HCV infection is treated today with combinations of direct-acting antiviral agents (DAAs), which target different steps of the HCV lifecycle. DAA combinations also present evidence of the trade-off (Table 1). Xiao *et al.* examined the effect of inhibitors of HCV entry into cells when combined with other drugs [10]. They quantified synergy using the combination index, $CI = \frac{D_1}{(D_1)_\varepsilon} + \frac{D_2}{(D_2)_\varepsilon}$, where $(D_1)_\varepsilon$ and $(D_2)_\varepsilon$ are the concentrations (or dosages) of drugs 1 and 2 that individually yield efficacy ε, typically following the median-effect equation (see Equation I in Box 1), and D_1 and D_2 are their concentrations that yield the same efficacy in combination. $CI < 1$ implies synergy between the drugs; the smaller the CI, the greater the extent of the synergy. Xiao *et al.* found that CI often increased with ε [10]. For instance, with the drugs boceprevir and erlotinib CI increased from 0.25 to 0.75 as ε increased from 0.5 to 0.9, where ε is defined as the fraction of infection events prevented by the drug(s). Thus, synergy decreased as efficacy increased. This trend was seen with several DAA combinations and with many DAAs in combination with monoclonal antibodies blocking HCV entry (Table 1) [10].

Some current antiretroviral drugs for HIV treatment also exhibit the trade-off (Table 1). Jilek *et al.* [5] quantified antiretroviral drug action using f_u, the fraction of infection events unaffected by the drug(s). The efficacy of the drug(s) is thus $\varepsilon = 1 - f_u$. From the data reported in Jilek *et al.* [5], we found that for the drugs nevirapine and zidovudine, which interacted synergistically, as the concentrations decreased from the maximum levels studied, the efficacy (ε) decreased but Bliss synergy increased (Table 1). The same trend was observed for the drugs dolutegravir and tenofovir [11] (Table 1). The synergy–efficacy trade-off is thus evident in these drug combinations. More recently, stochastic simulations of the effect of HIV latency-reversing agents too have argued that increasing Bliss synergy beyond a point compromises efficacy [12].

Finally, we present evidence of the trade-off in anticancer drugs. In a recent study, several chondrosarcoma cell lines resistant to chemotherapy were made sensitive to cisplatin by inhibiting the antiapoptotic protein Bcl-xl using the drug WEHI-539 [13]. Experiments used a fixed level of WEHI-539 and different levels of cisplatin, ranging from 0.39 to 100 μM. The level of Bliss synergy (β_B) was estimated as defined in Box 1. With several cell lines where synergy was observed, the maximum synergy occurred at intermediate drug, and therefore efficacy, levels (Table 1). For instance, β_B was highest at 12.5 μM cisplatin for the cell line SW1353 and at 6.25 μM cisplatin for the cell line L835 [13] (Table 1). Increasing the cisplatin level beyond this value increased efficacy but compromised synergy, reflecting the synergy–efficacy trade-off. In another study on adult T cell leukemia cell lines, ruxolitinib, an inhibitor of Janus kinase (JAK), was examined for its activity in combination with each of >450 potential drugs using high-throughput matrix screens [14]. The response in terms of cell viability relative to that in the absence of treatment was measured. For several drug combinations, as the combined efficacy (ε), defined as the decrease in cell viability, increased, Bliss synergy decreased. For instance, for the combination of ruxolitinib and panobinostat, as ε increased from 0.89 to 0.96, β_B decreased from 0.14 to 0.08 (Table 1). Similarly, for the combination of ruxolitinib and withaferin A, a gain in ε from 0.32 to 0.47 was associated with a loss in β_B from 0.22 to 0.12 (Table 1). Thus, examples abound of the synergy–efficacy trade-off across diseases and drug combinations.

Origin of the Synergy–Efficacy Trade-Off

The numerous examples above of the synergy–efficacy trade-off, across diseases and drug combinations, suggest that the trade-off is an inherent characteristic of synergistic drug combinations and is independent of the specific mechanisms of the drug interactions yielding synergy. In accordance, we show that a generalized, mechanism-agnostic model of drug interactions recapitulates the synergy–efficacy trade-off (Box 1). While efficacy increases monotonically with drug levels, synergy first rises and then falls (see Figure I in Box 1). These trends can be understood as follows. When the drugs are at low concentrations, minimal interactions are expected to occur between the

Box 1. A Generalized Model of Drug Interactions Predicts the Synergy–Efficacy Trade-Off

Consider drugs 1 and 2, used at dosages D_1 and D_2, acting with efficacies ε_1 and ε_2, respectively. Let their dose–response relationships follow the median-effect equation [2,5],

$$\varepsilon_1 = \frac{\varepsilon_1^{max}\left(\frac{D_1}{IC_{50}^1}\right)^{m_1}}{1+\left(\frac{D_1}{IC_{50}^1}\right)^{m_1}}; \varepsilon_2 = \frac{\varepsilon_2^{max}\left(\frac{D_2}{IC_{50}^2}\right)^{m_2}}{1+\left(\frac{D_2}{IC_{50}^2}\right)^{m_2}}, \quad [I]$$

where: $\varepsilon_i^{max}(i = 1, 2)$ represents the maximum efficacy of drug i, attained at large values of D_i; $IC_{50}{}^i$, the potency of drug i, represents the value of D_i at which $\varepsilon_i = 0.5\varepsilon_i^{max}$; and m_i, the slope parameter, defines the steepness of the dose–response curve near $D_i = IC_{50}{}^i$. We let the drugs exhibit synergistic interactions. Thus, we write the combined efficacy of the drugs as

$$\varepsilon_{comb} = \frac{\varepsilon_1^{max}\left(\frac{D_1}{IC_{50}^{12}}\right)^{m_1} + \varepsilon_2^{max}\left(\frac{D_2}{IC_{50}^{21}}\right)^{m_2} + \left(\varepsilon_1^{max} + \varepsilon_2^{max} - \varepsilon_1^{max}\varepsilon_2^{max}\right)(1+\alpha)\left(\frac{D_1}{IC_{50}^{12}}\right)^{m_1}\left(\frac{D_2}{IC_{50}^{21}}\right)^{m_2}}{1+\left(\frac{D_1}{IC_{50}^{12}}\right)^{m_1} + \left(\frac{D_2}{IC_{50}^{21}}\right)^{m_2} + (1+\alpha)\left(\frac{D_1}{IC_{50}^{12}}\right)^{m_1}\left(\frac{D_2}{IC_{50}^{21}}\right)^{m_2}}. \quad [II]$$

Here, $IC_{50}^{12} = IC_{50}^1 / \left(1 + \gamma_{12}\frac{D_2}{IC_{50}^2}\right)$ is the potency of drug 1 in the presence of drug 2. Similarly, $IC_{50}^{21} = IC_{50}^2 / \left(1 + \gamma_{21}\frac{D_1}{IC_{50}^1}\right)$. The parameter γ_{12} determines the strength of the effect of drug 2 on the potency of drug 1. γ_{21} is analogously defined. α is a measure of the effect of the interactions between the drugs on their combined efficacy (see below).

Equation II has a structure similar to the generalized 2D Hill equation derived recently to quantify drug interactions [3] and reduces to expected forms under several limiting scenarios. When a single drug is used, ε_{comb} reduces to the single-drug efficacy; that is, $\varepsilon_{comb} = \varepsilon_1$ when $D_2 = 0$. When $\alpha = \gamma_{12} = \gamma_{21} = 0$, indicating no interactions, Bliss independence results: $\varepsilon_{comb} = \varepsilon_B = \varepsilon_1 + \varepsilon_2 - \varepsilon_1\varepsilon_2$. With $\alpha > 0$ and $\gamma_{12} = \gamma_{21} = 0$, the drugs exhibit synergy in efficacy. When $\gamma_{12} > 0$ or $\gamma_{21} > 0$ or both, but $\alpha = 0$, the drugs exhibit synergy in potency. (When any of the latter constants become negative, the drugs exhibit antagonistic interactions, not considered here.)

We quantified synergy using both Bliss synergy, $\beta_B = \varepsilon_{comb} - \varepsilon_B$, and Loewe synergy, $\beta_L = \varepsilon_{comb} - \varepsilon_L$, where the efficacy due to Loewe additivity, ε_L, is obtained by solving [2,19]

$$\frac{D_1}{IC_{50}^1}\left(\frac{\varepsilon_L}{\varepsilon_1^{max} - \varepsilon_L}\right)^{-1/m_1} + \frac{D_2}{IC_{50}^2}\left(\frac{\varepsilon_L}{\varepsilon_2^{max} - \varepsilon_L}\right)^{-1/m_2} = 1. \quad [III]$$

We varied D_1 and D_2 and computed the efficacy, ε_{comb}, and the extent of synergy, β_B and β_L, using the expressions above for parameters representing synergy in efficacy or potency (Figure IA,B). As expected, ε_{comb} increased with D_1 and D_2. Both β_B and β_L, however, varied nonmonotonically with D_1 and D_2, rising from low values initially, attaining a peak, and then decreasing as ε_{comb} approached its maximum. The latter decrease in β with increase in ε_{comb} reflects the synergy–efficacy trade-off.

We found that, with sufficient data, the model could fit experimental measurements of ε_{comb} versus D_1 and D_2 well and with the resulting best-fit parameter estimates capture the observed synergy–efficacy trade-off (Figure IC).

We can explain the trends leading up to the synergy–efficacy trade-off analytically under certain conditions. For synergy in efficacy ($\alpha > 0; \gamma_{12} = \gamma_{21} = 0$), combining Equations I and II yields

$$\varepsilon_{comb} = \frac{\varepsilon_1^{max}\varepsilon_2^{max}\varepsilon_B + \varepsilon_B^{max}\alpha\varepsilon_1\varepsilon_2}{\varepsilon_1^{max}\varepsilon_2^{max} + \alpha\varepsilon_1\varepsilon_2} \text{ and } \beta_B = \frac{\left(\varepsilon_B^{max} - \varepsilon_B\right)\alpha\varepsilon_1\varepsilon_2}{\varepsilon_1^{max}\varepsilon_2^{max} + \alpha\varepsilon_1\varepsilon_2}, \text{ where } \varepsilon_B^{max} = \varepsilon_1^{max} + \varepsilon_2^{max} - \varepsilon_1^{max}\varepsilon_2^{max}. \quad [IV]$$

Thus, β_B is small when ε_1 and ε_2 are small, reflecting dosages too low for significant interactions between the individual drug effects. As ε_1 and ε_2 rise, interactions become significant and β_B rises. When ε_1 and ε_2 approach their respective maximum values, so does ε_B, driving β_B to zero regardless of α. Similarly, for synergy in potency, where drug 1 potentiates drug 2 ($\alpha = 0; \gamma_{12} = 0; \gamma_{21} > 0$), we can show, when $m_1 = m_2 = 1$, that

$$\varepsilon_{comb} = \frac{\varepsilon_1^{max}\varepsilon_2^{max}\varepsilon_B - \varepsilon_1\varepsilon_2\varepsilon_2^{max}(1-\gamma_{21})(1-\varepsilon_1) - \varepsilon_1^2\left(\varepsilon_2^{max} - \gamma_{21}\varepsilon_2\right)}{\varepsilon_1^{max}\varepsilon_2^{max} - \varepsilon_1\varepsilon_2^{max} + \gamma_{21}\varepsilon_1\varepsilon_2} \quad [V]$$

and

$$\beta_B = \frac{\left(\varepsilon_2^{max} - \varepsilon_2\right)(1-\varepsilon_1)\gamma_{21}\varepsilon_1\varepsilon_2}{\varepsilon_1^{max}\varepsilon_2^{max} - \varepsilon_1\varepsilon_2^{max} + \gamma_{21}\varepsilon_1\varepsilon_2}, \quad [VI]$$

which also show ε_{comb} increasing to ${\varepsilon_B}^{max}$ and β_B decreasing to zero when ε_1 and ε_2 approach their respective maxima. For arbitrary m_1 and m_2 or for Loewe synergy, analytical expressions are not readily derived. Numerical solutions, however, do indicate the trade-off in these latter scenarios (Figure I).

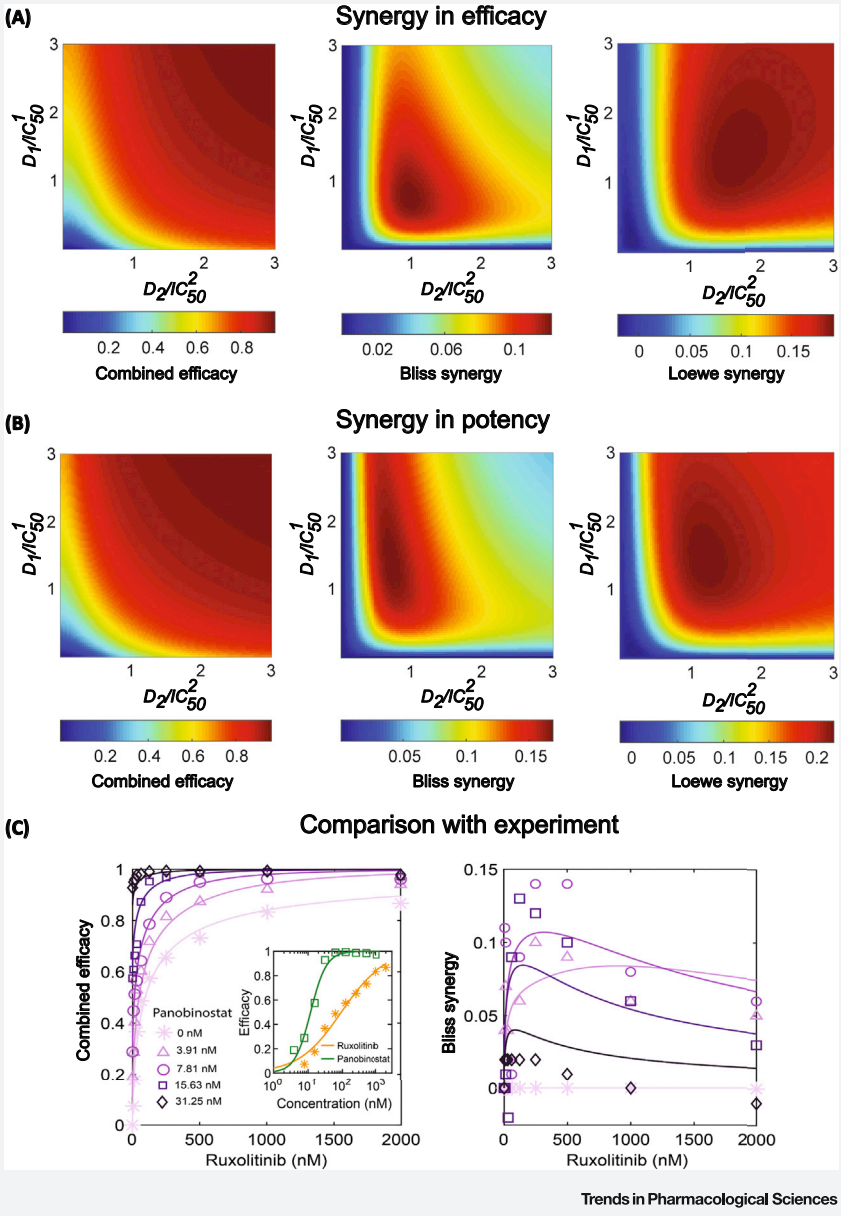

Figure I. Model Predictions of the Synergy–Efficacy Trade-Off and Comparison with Experiment.

(A) Heat maps showing the combined efficacy, ε_{comb} (left), and the corresponding extent of Bliss synergy, β_B (middle), and Loewe synergy, β_L (right), as functions of the dosages of the two drugs, calculated using the generalized model when synergy is in efficacy. (B) Corresponding heat maps when synergy is in potency. Parameters used are $m_1 = 1$, $m_2 = 2$, ${\varepsilon_1}^{max} = 0.9$, and ${\varepsilon_2}^{max} = 0.8$. Further, $\alpha = 2.5$ and $\gamma_{12} = \gamma_{21} = 0$ (A) and $\alpha = 0$, $\gamma_{12} = 0.8$, and $\gamma_{21} = 0.7$ (B). (C) Fits of the model to experimental data for the efficacy of ruxolitinib (drug 1) and panobinostat (drug 2) against adult T cell leukemia in cell lines (left) and resulting predictions of Bliss synergy (right). Experimental data [14] are in symbols and model fits and predictions are in lines. Fits were obtained by first considering single-drug data (left inset), which yielded $m_1 = 0.70 \pm 0.15$, $IC_{50}{}^1 = 93 \pm 25$ nM, $m_2 = 1.9 \pm 0.5$, and $IC_{50}{}^2 = 12 \pm 2$ nM. The observed efficacies at high concentrations suggested ${\varepsilon_1}^{max} = {\varepsilon_2}^{max} = 1$, which we fixed. With these parameters, we then fit the efficacy data of the combination at all of the dosages employed, which

yielded $\gamma_{12} = 0.9 \pm 0.7$ and $\gamma_{21} = 0.24 \pm 0.16$ when we fixed $\alpha = 0$. (Letting α be adjustable yielded fits with arbitrarily small values of α, suggesting $\alpha = 0$, but compromised confidence levels.) With all of the parameters thus identified, we used the model to predict the extent of Bliss synergy for the different combinations studied, which compared well with experimental estimates (right). The trade-off is evident as the synergy peaks at intermediate concentrations of the two drugs.

entities, such as receptors or pathways, targeted by the drugs. The combination thus exhibits Bliss independence. As the concentrations rise, the chance of interactions increases and the drugs exhibit synergy. The extent of synergy thus increases with concentration and hence efficacy. Drug combinations do not reflect the trade-off in this regime. Beyond a point, however, efficacy continues to rise with drug levels but synergy drops. Synergy requires that an effect beyond the independent effects of drugs appears. When a drug is used at a high dosage, its independent effect can elicit near-maximal efficacy, such as maximal blocking of a target receptor or maximal excitation of a downstream pathway, leaving little room for the other drug to improve its activity. The scope for synergy thus shrinks, explaining the trade-off. This general explanation of the trade-off is also borne out in specific cases where the mechanisms of drug interactions are explicitly incorporated in detailed mathematical models, as with interferon and ribavirin [9] and HIV latency-reversing agents [12].

Concluding Remarks

Drug levels that maximize synergy need not simultaneously maximize efficacy. While synergy is desirable, it cannot come at the cost of efficacy. We found evidence of the synergy–efficacy trade-off from studies that examined drug interactions over concentration ranges wide enough to realize the trade-off. The search for maximum synergy must therefore be constrained by the desired efficacy, especially when side-effects are manageable. Such constrained optimization has been proposed earlier for HIV latency-reversing agents [12]. Because the trade-off is independent of the specific mechanisms underlying synergy, future studies may seek it in drug combinations beyond our study.

Often, a critical level of efficacy to achieve the desired therapeutic effect can be estimated from independent considerations. For instance, a critical efficacy can be defined based on the within-host basic reproductive ratio of viruses, a quantitative measure of virulence, to elicit adequate control of viral infections using antiviral therapies [15]. If the critical efficacy is such that high synergy is possible without compromising efficacy, optimal combinations may benefit from incorporating synergistic drugs. If the critical efficacy is high enough that little room for synergy is left, screening for optimal drug combinations need not prefer synergistic drugs.

It is important to note that drugs acting independently may appear synergistic at the population level because different individuals may respond differently to the drugs in a combination [16]. Different cells in an individual can also respond differently to different drugs [17]. Our arguments of the trade-off apply to drugs manifesting intrinsic synergistic interactions. Finally, we recognize that synergistic drug combinations may accelerate the evolution of multidrug resistance, and conditions that preclude such evolution are screened for in optimizing treatments [18]. Future efforts to optimize drug combinations would similarly benefit from accounting for the synergy–efficacy trade-off.

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References

1. Zimmermann, G.R. *et al.* (2007) Multi-target therapeutics: when the whole is greater than the sum of the parts. *Drug Discov. Today* 12, 34–42
2. Foucquier, J. and Guedj, M. (2015) Analysis of drug combinations: current methodological landscape. *Pharmacol. Res. Perspect.* 3, e00149
3. Meyer, C.T. *et al.* (2019) Quantifying drug combination synergy along potency and efficacy axes. *Cell Syst.* 8, 97–108.e16
4. Frei, E., III *et al.* (1998) The relationship between high-dose treatment and

combination chemotherapy: the concept of summation dose intensity. *Clin. Cancer Res.* 4, 2027–2037
5. Jilek, B.L. *et al.* (2012) A quantitative basis for antiretroviral therapy for HIV-1 infection. *Nat. Med.* 18, 446–451
6. Koizumi, Y. *et al.* (2017) Quantifying antiviral activity optimizes drug combinations against hepatitis C virus infection. *Proc. Natl. Acad. Sci. U. S. A.* 114, 1922–1927
7. Nowak-Sliwinska, P. *et al.* (2016) Optimization of drug combinations using feedback system control. *Nat. Protoc.* 11, 302–315
8. Preuer, K. *et al.* (2017) DeepSynergy: predicting anti-cancer drug synergy with deep learning. *Bioinformatics* 34, 1538–1546
9. Dixit, N.M. *et al.* (2004) Modelling how ribavirin improves interferon response rates in hepatitis C virus infection. *Nature* 432, 922–924
10. Xiao, F. *et al.* (2015) Synergy of entry inhibitors with direct-acting antivirals uncovers novel combinations for prevention and treatment of hepatitis C. *Gut* 64, 483–494
11. Laskey, S.B. and Siliciano, R.F. (2016) Quantitative evaluation of the antiretroviral efficacy of dolutegravir. *JCI Insight* 1, e90033
12. Gupta, V. and Dixit, N.M. (2018) Trade-off between synergy and efficacy in combinations of HIV-1 latency-reversing agents. *PLoS Comput. Biol.* 14, e1006004
13. de Jong, Y. *et al.* (2018) Bcl-xl as the most promising Bcl-2 family member in targeted treatment of chondrosarcoma. *Oncogenesis* 7, 74
14. Zhang, M. *et al.* (2015) Selective targeting of JAK/STAT signaling is potentiated by Bcl-xL blockade in IL-2-dependent adult T-cell leukemia. *Proc. Natl. Acad. Sci. U. S. A.* 112, 12480–12485
15. Nowak, M.A. and May, R.M. (2000) *Virus Dynamics: Mathematical Principles of Immunology and Virology*, Oxford University Press
16. Palmer, A.C. and Sorger, P.K. (2017) Combination cancer therapy can confer benefit via patient-to-patient variability without drug additivity or synergy. *Cell* 171, 1678–1691.e13
17. Padmanabhan, P. and Dixit, N.M. (2015) Modeling suggests a mechanism of synergy between hepatitis C virus entry inhibitors and drugs of other classes. *CPT Pharmacometrics Syst. Pharmacol.* 4, 445–453
18. Yeh, P.J. *et al.* (2009) Drug interactions and the evolution of antibiotic resistance. *Nat. Rev. Microbiol.* 7, 460
19. Tang, J. *et al.* (2015) What is synergy? The Saariselka agreement revisited. *Front. Pharmacol.* 6, 181