Rational combination of dual PI3K/mTOR blockade and Bcl-2/-xL inhibition in AML

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ACUTE MYELOID LEUKEMIA (AML) is diagnosed in more than 250,000 adults worldwide each year, the majority of whom are elderly (111). Induction chemotherapy with “7+3,” consisting of cytarabine and an anthracycline such as idarubicin or daunorubicin (or the anthracenedione mitoxantrone), first described over 40 years ago (140), has remained the standard approach to initial treatment and is usually followed by consolidation chemotherapy once morphologic remission is achieved, with bone marrow transplantation playing a potentially curative role in selected cases (9, 59). Despite substantial progress in recent years in advancing our understanding of the biology of AML, in large part due to the availability of mutational screening and whole genome/exome sequencing (12, 95), there has been little improvement in therapy, with cure remaining elusive for the large majority of patients (10). The outlook is particularly dismal for elderly patients (29) and those with relapsed/refractory disease (35). The inability of traditional chemotherapeutics to kill the quiescent, self-renewing leukemic stem cell (LSC) population (68) is potentially a major reason why cure has not been consistently achieved. It is believed that novel strategies for targeting AML must target this LSC population (86). Recent insights into the nature of oncogene addiction (115) have also revealed that multiple survival signaling pathways cooperate to promote transformed cell survival (116). A corollary of this concept is that multiple pathways, rationally selected for each tumor type and ideally personalized to an individual patient’s cancer, must be coordinately disrupted to optimize transformed cell killing (58, 75). An attempt was recently made (101) to target three such critical and interdependent survival pathways in AML cells [the Bcl-2 (B-cell lymphoma 2) family of antiapoptotic proteins, and the PI3K/Akt/mTOR (phosphatidylinositol-3-kinase/Akt/mammalian target of rapamycin) and mitogen-activated protein kinase kinase (MEK)/ERK signaling pathways] in an effort to prime them for apoptosis (132).
BCL-2 FAMILY OF PRO- AND ANTIAPOPTOTIC PROTEINS

The Bcl-2 family proteins control the central, evolutionarily conserved pathway for regulating programmed cell death, i.e., the “intrinsic,” or mitochondrial pathway of apoptosis (106). In essence, the Bcl-2 family of proteins consists of the “multi-domain” proapoptotic proteins [Bcl-2, Bcl-xL, Bcl-w, Bfl-1 (A1), and Mcl-1 (myeloid cell leukemia-1)] and the apoptosis “effectors” Bax and Bak, and the “activator” (Bim, Bid, and perhaps Puma) or “sensitizer” (Bad, Bik, Noxa, Hrk, Bmf, Puma) “BH3-only” proteins (24). Bax and Bak directly participate in the formation of pores in the mitochondrial outer membrane, triggering mitochondrial outer membrane permeabilization (MOMP), the central event that controls cellular commitment to death via apoptosis, and the activator BH3-only proteins interact with and activate Bax and Bak directly to this end (24). The antiapoptotic Bcl-2 family proteins prevent MOMP by sequestering the apoptosis activators and effectors by binding to their BH3 domain, a phenomenon that is competitively inhibited by the proapoptotic sensitizer BH3-only proteins (24). The Bcl-2 family proteins operate as nodal points at the convergence of multiple pathways (106), and their central role in triggering the final common pathway of apoptosis, characterized by caspase activation, makes them particularly attractive drug targets (67). Multiple studies have implicated the role of Bcl-2 family proteins in AML pathogenesis (20, 42, 50), prognosis (27, 48, 131), and resistance to chemotherapy (11, 66, 69, 118). Small-molecule “BH3-mimetics” that inhibit the antiapoptotic functions of Bcl-2 and Bcl-xL have, therefore, been developed (91, 121, 129). Significantly, however, these drugs do not inhibit Mcl-1, which may be more critical for the development and maintenance of AML than Bcl-2 and Bcl-xL (42), and an essential effector of FLT3-ITD (fms-like tyrosine kinase - internal tandem duplication)-mediated drug resistance (60) and stem cell survival (144) in AML. Not surprisingly, numerous studies have demonstrated Mcl-1, a short-lived protein critically dependent upon active transcription and translation for its maintenance (55), to be a key determinant of resistance to the BH3-mimetic ABT-737 (63, 72, 126, 130, 141). Mcl-1 is an inducible protein (38) that also functions as a stress “sensor” to coordinately regulate both apoptosis and autophagy (41). Another Bcl-2 family protein involved in determining “Bcl-2 dependence” of certain leukemias [e.g., chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia] and, hence, their sensitivity to ABT-737 is the proapoptotic BH3-only protein, Bim (25, 26). Furthermore, complex interactions between, and not simply expression patterns of Bcl-2 family proteins, particularly those involved in Bim, which binds to all three major antiapoptotic proteins (16, 43), have been shown to be critical factors underlying sensitivity or resistance to ABT-737 (18, 87). Several studies have used the aforementioned principles, viz. downregulation of Mcl-1 and upregulation of Bim, to design strategies that synergistically enhance the lethality of ABT-737 and other BH3-mimetics toward AML cells (17, 64, 102, 146), thus simultaneously targeting multiple arms of the apoptotic regulatory machinery (23).

PI3K/AKT/mTOR SIGNALING PATHWAY

The PI3K/AKT/mTOR pathway is a cellular growth, proliferation, motility, and survival signaling axis (13) that represents one of the most frequently dysregulated pathways in cancer (22), including AML (83), where activation of the pathway has been shown to be required for cell survival (138, 139). Three classes of PI3K exist, of which class Iα PI3Ks are most clearly implicated in human cancers and targeted by current pharmacologic PI3K inhibitors (31). Class Iα PI3Ks are heterodimers that consist of a p85 regulatory and a p110 catalytic subunit (22, 31). In response to extracellular cues [usually growth factor stimulation via receptor tyrosine kinase (RTK) signaling], the p85 regulatory subunit binds to RTKs and/or adapters, relieving its inhibition of the p110 catalytic subunit and recruiting class Iα PI3Ks to the plasma membrane, where their substrate, phosphatidylinositol-4,5-bisphosphate (PIP_{2}), resides (22, 31). PI3K then phosphorylates PIP_{2} at the 3-hydroxyl position to produce phosphatidylinositol-3,4,5-trisphosphate (PIP_{3}), while the tumor suppressor PTEN (phosphatase and tensin homolog deleted on chromosome 10) terminates PI3K-dependent signaling by catalyzing the reverse reaction (22, 31, 112). PIP_{3} brings two serine/threonine kinases, Akt/protein kinase B and phosphoinositide-dependent kinase 1 (PDK_{1}), into close proximity on the cell membrane, upon which Akt is activated by PDK_{1} by phosphorylation at Thr308, while full activation requires Ser473 phosphorylation by mTORC2 (mTOR containing protein complex 2) (22, 31). Akt in turn regulates, through [generally inhibitory (13)] phosphorylation, a wide range of target proteins that control cell proliferation, survival, growth, and other processes: these include the proapoptotic Bcl-2 family proteins Bim, Bad, and Bax; forkhead box O (FOXO) transcription factors (which mediate apoptosis by activating the transcription of pro-apoptotic genes such as FasL and Bid); murine double minute 2 homolog, the negative regulator of the tumor suppressor p53; GSK3 (glycogen synthase kinase 3) isoforms (which downregulate cyclin D1 and Myc); procaspase-9; I-kappa B kinase, the negative regulator of the prosurvival transcription factor NF-kB; TSC2 (tuberous sclerosis complex 2) and proline-rich Akt substrate of 40 kDa, critical negative regulators of mTORC1 (mTOR containing complex 1) signaling; the endogenous cyclin-dependent kinase (CDK) inhibitor p27_{kip1}; and the DNA damage checkpoint kinase Chk1 (74, 78).

RATIONALE FOR DUAL PI3K AND mTOR BLOCKADE IN AML

Dysregulation of the PI3K/Akt/mTOR pathway in AML stems from multiple abnormalities, including PTEN loss (112), RTK activation [e.g., FLT3-ITD (7), KIT (88)], Ras, insulin-like growth factor-1 and its receptor (IGF-1/IGF-1R) (113), or activating mutations or overexpression of PI3K (51) or Akt (83). In AML, Akt activation (phosphorylation at Thr308/Ser473) variably occurs in 50–80% of patients, despite the rarity of activating mutations of Akt or PI3K or of PTEN loss (39, 82, 85, 122). Consequently, there is considerable interest in therapeutically targeting the PI3K/Akt/mTOR pathway in AML (34, 81). Both PI3K (47) and mTOR inhibitors have been shown to inhibit LSC survival (142, 143) and the latter to block Mcl-1 translation (6, 97), making them attractive candidates for AML therapy. Importantly, mTORC1 is a major downstream effector of Akt that is often not only under the control of PI3K/Akt signaling; GSK3 and AMP-activated protein kinase (AMPK), besides the two effector kinases downstream of RAS,

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ERK and ribosomal protein S6 kinase (RSK), can also phospho-
ylate TSC2 and thus effectively promote mTORC1 activ-
ity (4, 76, 77, 125). This argues for a therapeutic advantage for
dual PI3K/mTOR inhibitors over agents that inhibit only PI3K
(31). Conversely, currently approved mTOR inhibitors (tem-
sirolimus, everolimus) often lead to feedback activation of
PI3K/Akt and MEK/ERK through induction of IRS-1 (insulin
receptor substrate 1) and Grb10, a phenomenon that may
compromise their antitumor activity (14, 53, 92, 110, 145).
This has been demonstrated preclinically to be the case in
AML and provides a rationale for therapeutic inhibition of both
PI3K/Akt and mTOR (127). Indeed, the dual PI3K/mTOR
inhibitors PI-103 (94) and NVP-BEZ235 (15) display substan-
tial activity against AML cell lines and primary AML samples.
Finally, through a poorly understood mechanism (5, 30, 61),
PI3K inhibitors may disrupt the complementary Ras/Raf/
MEK/ERK survival signaling pathway, activated in >80%
of AML samples (107), in AML cells (104, 124), in sharp contrast
to its activation in other tumor types by PI3K (114) and mTOR
inhibitors (14, 62), and by the Akt inhibitor perifosine in AML
(103) and multiple myeloma cells (49). The combination of
PI3K or mTOR inhibitors with MEK inhibitors to overcome
this paradoxical activation is, in fact, a well-described syner-
gistic strategy (32, 45, 117, 120, 134). It appears that, at least
in AML cells, dual PI3K/mTOR inhibitors might be able to
accomplish the task of cotargeting the PI3K/Akt/mTOR and
MEK/ERK survival signaling pathways without the need for a
MEK inhibitor.

RATIONAL FOR COMBINING DUAL PI3K/MTOR INHIBITORS WITH BH3-MIMETICS IN AML CELLS

The PI3K/Akt/mTOR and MEK/ERK survival signaling
pathways extensively regulate the Bcl-2 family proteins and
are thus intimately linked to the apoptotic pathways. Akt
upregulates Bcl-2 and Mcl-1 via cyclic adenosine monophos-
phate response element binding protein (CREB) (80, 98, 133).
The disposition of both pro (e.g., Bad, Bim)- and antiapoptotic
(e.g., Mcl-1) proteins is regulated not just by Akt but also by
ERK1/2 (54, 73, 117). For example, phosphorylation at Ser55/
65/100 (by ERK1/2) and Ser87 (by Akt) leads to Bim (-EL)
degradation (96, 99). Highly synergistic interactions have been
reported between Akt and MEK inhibitors in promoting AML
cell death through Bim- and Mcl-1 (but not Bad)-dependent
mechanisms (100). Notably, Mcl-1 and Bim expression are
tightly regulated by both the PI3K/Akt/mTOR and MEK/ERK
pathways. While PI3K drives Mcl-1 transcription through a
CREB-dependent process, mTOR regulates its translation, and
the Akt/GSK3 axis and the E3 ubiquitin ligase SCF/FB77
(SKP1-cullin-1-F-box complex that contains FB77 as the
F-box protein) control its posttranslational proteasomal degra-
dation (52, 56, 133, 135). Similarly, ERK may activate Mcl-1
transcription through SRF/Elk-1, while also slowing turnover
of the normally rapidly degraded Mcl-1 protein by phosphor-
ylating it at Thr163 (28, 128). As discussed above, regulation
of Bim expression and function by the PI3K/Akt and MEK/
ERK pathways occurs at the transcriptional level through
FOXO3a (33, 123) and particularly at the posttranslational
level through phosphorylations by Akt (99) and ERK (46).
Finally, it is important to consider the interplay between the
MEK/ERK and PI3K/Akt/mTOR pathways: thus, as alluded to
earlier, ERK phosphorylation and inactivation of TSC2 remove
the latter’s inhibitory effects on mTOR signaling, cell prolif-
eration, and oncogenic transformation (76).

It follows from the above discussion that the combination of
a dual PI3K/mTOR inhibitor with a BH3-mimetic that antag-
onizes the antiapoptotic functions of Bcl-2 and Bcl-xL repre-
sents, at least theoretically, a particularly potent synergistic
strategy against AML cells, especially those that are FLT3-/ITD+,
including LSCs. First, such a strategy would interrupt
two major and complementary signaling pathways (viz., PI3K/
Akt/mTOR and Ras/Raf/MEK/ERK) considered critical for
AML cell survival while avoiding undesirable feedback activa-
tion of PI3K/Akt and ERK1/2. Second, PI3K/mTOR inhib-
tors would be expected to be particularly effective at down-
regulating Mcl-1, central to AML development and mainte-
nance and the main determinant of resistance to ABT-737,
given that they act at three separate levels (viz., transcriptional,
translation, and posttranslational, via GSK3-mediated degra-
dation) to accomplish this. Based on this strong theoretical
foundation (Fig. 1), the effects of concomitant PI3K/mTOR
and Bcl-2/Bcl-xL inhibition were recently examined in AML
cell lines, patient-derived blasts, and xenograft models of AML
(101). The findings of these studies are summarized below.

Studies conducted on AML cells using tet-inducible short
hairpin RNA constructs directed against Akt or Bcl-2 and
Bcl-xL individually or together, as well as employing pharma-
cologic inhibitors (e.g., NVP-BEZ235/PI-103 and ABT-737)
revealed that the PI3K/Akt/mTOR pathway and Bcl-2/Bcl-xL
play important coordinate roles in protecting leukemia cells
from lethality. Specifically, genetic or pharmacologic interven-
tions simultaneously inhibiting the PI3K/Akt/mTOR pathway
and disabling Bcl-2/Bcl-xL dramatically enhanced leukemic
cell death, with minimal toxicity toward normal CD34+ he-
matopoietic progenitors. These findings were recapitulated in
vivo in an AML xenograft model with little toxicity. Mcl-1

![Fig. 1. Hypothetical model of interactions between phosphatidylinositol-3-
kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway inhibi-
tors and Bcl-2/-xL antagonists.](http://physiolgenomics.physiology.org/)
downregulation resulted from PI3K/mTOR inhibition, at least in part through GSK3 activation, which promotes the proteasomal degradation of Mcl-1. Although NVP-BEZ235 alone downregulated Mcl-1, it did not significantly trigger cell death, underscoring the importance of concomitant Bcl-2/Bcl-xL inhibition, as all three major antiapoptotic proteins sequester the apoptosis effectors Bax and Bak. Significantly, release of Bax and Bak from Mcl-1, Bcl-2, and Bcl-xL was observed. Another novel finding was a marked increase in Bim binding to Bcl-2 and Bcl-xL in response to PI3K/mTOR inhibition, a phenomenon effectively abolished by ABT-737. Presumably Bim, liberated from these two antiapoptotic proteins, as well as Mcl-1 (due to downregulation), triggered apoptosis by activating Bax and Bak. A particularly intriguing observation was an apparent correlation between responses to combined treatment with PI3K/mTOR inhibitors and ABT-737 and baseline Akt activation in primary AML blasts. Specifically, four of six specimens analyzed responded to the treatment, and all exhibited basal Akt phosphorylation. In contrast, basal Akt phosphorylation was not detected in nonresponding specimens or in normal CD34+ cells. This raises the possibility that the former cells were addicted to the PI3K/Akt/mTOR pathway and hence vulnerable to its inhibition. Definitive answers to this question will require analysis of a considerably larger number of specimens.

A major challenge with inhibitors of the PI3K/Akt/mTOR pathway has been delineation of their pharmacodynamic effects; i.e., determining whether or not the administration of these agents leads to target inhibition in vivo (109). Biomarkers that have been used to this end have included phosphorylation of Akt and its substrate Akt1S1 (also known as PRAS40), phosphorylation of eukaryotic translation initiation factor 4E-binding protein 1 (4EBP1), and phosphorylation of RPS6, the proliferation marker Ki-67, and the apoptosis marker TUNEL (109). Of note, however, RPS6 and 4EBP1 can also be regulated by Ras/Raf/MEK/ERK/mTORC1 signaling, thereby confounding assessment of the true pharmacodynamic effects of PI3K/Akt/mTOR pathway inhibitors. In the studies discussed above (101), Western blot analysis conducted on excised tumor tissue from treated mice revealed that NVP-BEZ235 alone or in combination elicited basal Akt phosphorylation, analogous to in vitro observations, thus confirming on-target pharmacodynamic activity of this novel drug combination in vivo in murine xenograft models of AML.

### CLINICAL CONSIDERATIONS

Various Bcl-2 family and PI3K/mTOR inhibitors have been studied in clinical trials, including in patients with AML. Table 1, either alone or in combination with standard chemotherapy. To date, however, agents from these classes have not been studied in combination in AML. Among the Bcl-2 family inhibitors, GX15–070 (obatoclax, Teva), a pan-BH-3 mimetic that is no longer in development, was shown to induce apoptosis in AML cells (57, 65). However, significant infusional central nervous system toxicity, including euphoria, somnolence, and ataxia, led to this agent being discontinued (57). G-3139 (oblimersen, Genta), an anti-sense oligonucleotide against Bcl-2 mRNA, failed to obtain regulatory approval despite promising results in the phase III setting in CLL (89, 90). A phase III randomized controlled trial of induction therapy with cytarabine and daunorubicin followed by consolidation therapy with high-dose cytotoxic chemotherapy and/or without oblimersen in older, previously untreated patients with AML failed to meet any of its endpoints (improvements in complete remission rate, overall survival, disease-free survival from date of complete remission, and event-free survival) (2, 79). Development of ABT-263 (navitoclax), the orally available analog of ABT-737 (129), despite evidence of promising single-agent clinical activity, e.g., in CLL (108), has been discontinued owing to concerns regarding dose-dependent thrombocytopenia (40, 137) secondary to on-target inhibition of Bcl-xL, critical for platelet survival (131). Initial reports on the successor molecule, ABT-199 (GDC-0199), a Bcl-2-specific BH3-mimetic that spares platelets (121), in CLL, a highly Bcl-2 dependent malignancy (25), have suggested robust activity (1). In an ongoing phase I trial (1) in patients with CLL/small lymphocytic lymphoma, the most common adverse effects reported were diarrhea (43%), neutropenia (37%), fatigue (33%), upper respiratory tract infection (33%), and cough (22%). A relatively high incidence of tumor lysis syndrome early in the trial was successfully addressed by lowering the dose of this very potent apoptosis inducer and by adopting a more cautious dose-escalation strategy (1). This agent has recently been shown to be remarkably effective in AML cell lines, primary patient samples, and murine primary

### Table 1. Dual PI3K/mTOR and Bcl-2 family inhibitors studied in clinical trials involving patients with AML

<table>
<thead>
<tr>
<th>Drug</th>
<th>Manufacturer</th>
<th>Class</th>
<th>Phase</th>
<th>Result</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>BEZ235</td>
<td>Novartis</td>
<td>dual PI3K and mTOR inhibitor</td>
<td>1</td>
<td>information not available</td>
<td>not applicable</td>
</tr>
<tr>
<td>G3139 (Oblimersen/Genasense/Augmerosen)</td>
<td>Genta</td>
<td>anti-sense oligonucleotide against Bcl-2</td>
<td>3</td>
<td>no differences in CR rate (48% vs. 52%; (P = 0.75)) or OS (0.83) between groups with or without oblimersen therapy</td>
<td>79</td>
</tr>
<tr>
<td>GX 15-070 (Obatoclax)</td>
<td>Teva</td>
<td>small molecule BH-3 mimetic against Bcl-2, Bcl-xL, Mcl-1, Bcl-w, Bfl-1/A1, and Bcl-B</td>
<td>2</td>
<td>no CRs</td>
<td>105</td>
</tr>
<tr>
<td>ABT-199 (GDC-0199)</td>
<td>Abbvie/Genentech</td>
<td>small molecule BH-3 mimetic against Bcl-2</td>
<td>2</td>
<td>information not available</td>
<td>not applicable</td>
</tr>
</tbody>
</table>

PI3K, phosphatidylinositol-3-kinase; mTOR, mammalian target of rapamycin; Bcl-2, B-cell lymphoma 2; AML, acute myeloid leukemia; CR, complete remission; OS, overall survival.
ex vivo studies in AML cells demonstrate great sensitivity to mimetics in order to trigger apoptosis (136). Recent data from and Bcl-xL, but not Bcl-2, by BH3-only proteins, or BH3-Bak is sequestered by and must be displaced from both Mcl-1. If such a case of ABT-737 occur, in light of evidence that proapoptotic function can trigger activation of compensatory prosurvival pathways that allows cells to bypass an inhibited kinase. Specifically, kinase inhibition can trigger activation of compensatory prosurvival pathways that relieve the neoplastic cell of its addiction to the kinase. Moreover, kinase mutations conferring resistance to pot inhibitors of FLT3 have already been described (119) and may contribute to the relatively transient nature of responses to this class of antileukemic agents (21, 71). Pending more definitive validation, the above findings with simultaneous PI3K/mTOR and Bcl-2/Bcl-xL blockade suggest novel candidate biomarkers (in this case, basal Akt activation) that may potentially be used in patients with AML (NCT01994837) and a phase II trial of ABT-199 (GDC-0199) in patients with AML (NCT01756118). Trials in other, predominantly solid, tumor types using inhibitors of the PI3K/Akt/mTOR pathway have shown that toxicities with this group of drugs are generally manageable. Hyperglycemia, hyperlipidemia, skin rashes, cytopenias, infections, gastrointestinal symptoms (nausea, vomiting, anorexia, dyspepsia, and diarrhea), mucositis, and stomatitis have been some of the more commonly reported adverse effects of these agents (109), two of which [the mTOR inhibitors temsirolimus (Torisel, Pfizer) and everolimus (Afinitor, Novartis)] are available commercially. While some of these are “off-target” effects, others have been thought to be directly related to their mechanism of action. In a large, phase II trial, the most frequent adverse effects of idelisib, the first PI3K (delta isoform-specific) inhibitor likely to be approved (36), were diarrhea, fatigue, nausea, cough, pyrexia, neutropenia, and transaminitis (44). Dual PI3K/mTOR inhibitors cause a wider range of off-target adverse effects, e.g., fatigue, but these, too, have generally been found to be acceptable in clinical trials (109). The toxicity profiles of PI3K/mTOR inhibitors and ABT-199 (GDC-0199) thus do overlap slightly, and carefully designed phase I dose-escalation trials will be necessary to optimize the clinical potential of this novel combination.

CONCLUSIONS

Recent approaches to the targeted therapy of AML have focused upon attempts to inhibit the kinase activity of mutated oncoproteins such as FLT3 (21, 71) and KIT (3, 8, 19) with small molecules. Although the field continues to evolve (70), currently, the number of such “actionable mutations” is small. An inherent problem with such approaches stems from the upstream location of these mutated oncoproteins and the marked redundancy of survival signaling pathways that allows cells to bypass an inhibited kinase. Specifically, kinase inhibition can trigger activation of compensatory prosurvival pathways that relieve the neoplastic cell of its addiction to the kinase. Moreover, kinase mutations conferring resistance resistant to the MEK1/2 inhibitor AZD6244 (ARRY-142886) is associated with weak ERK1/2 signalling and/or strong PI3K signalling in colorectal cancer cell lines. Int J Cancer 125: 2332–2341, 2009.


Regarding, rational combinations, such as with dual PI3K/mTOR inhibitors, are likely to prove necessary to further augment the activity of selective Bcl-2 antagonists like ABT-199 (GDC-0199) in AML for maximum therapeutic benefit.

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DISCLOSURES

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AUTHOR CONTRIBUTIONS

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Review

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