Supplementary Fig. 1 | a, Wright-Giemsa stained cells isolated from BM Chips at day 14 illustrating multilineage differentiation (red arrow, group of maturing erythroid cells; blue arrows, mature segmented neutrophils; gray arrow, macrophage; black arrows, megakaryocytes). b, Timecourse of CD34+ cell numbers and total colony forming units (CFUs) per culture when 1x10^4 CD34+ cells were seeded into BM Chips versus suspension and static gel co-cultures. CD34+ cells were quantified by flow cytometry. For CFU assays, cells from individual BM Chips or wells were harvested at the indicated timepoints, plated in methylcellulose cultures, and total colonies per BM Chip or well were counted (n=3-8 BM Chips or wells per timepoint except n=2 BM Chips at day 24; data pooled from 3 independent experiments; # and & indicate P<0.05 at the indicated timepoints for static gel and suspension cultures, respectively, compared to BM Chips). c, 1x10^4 CD34+ cells were seeded into suspension cultures, static gel co-cultures with BMSCs (-H), static gel co-cultures with BMSCs and HUVECs (+H), and BM Chips. After 14 days, cells from individual BM Chips or wells were harvested and plated in methylcellulose cultures. Myeloid (CFU-GM, CFU-G, and CFU-M) and erythroid (CFU-E and BFU-E) colonies were quantified (n=3-4 BM Chips or wells; data from 1 experiment; p-values for each group vs BM Chips is indicated). d, Graph of CD34+ CD38low progenitors over time (left) and representative flow cytometry plots at day 10 (right) in BM Chips or static gel co-cultures in a 96 well plate seeded with equivalent numbers of CD34+ cells and BMSCs (n=3-10 chips or wells per timepoint; data pooled from 4 independent experiments). e, Total, CD34+, neutrophil and erythroid cell numbers on days 14 and 28 in static gel co-cultures (CD34+ cells and BMSCs) with or without HUVECs (n=3 wells per timepoint). f,g Numbers of immature CD16lo neutrophils, immature E1 (CD71+CD235-) erythroid cells, total neutrophils, and total erythroid cells in the BM Chip, standard 96-well plate suspension cultures (CD34+ cells alone), or static 3D gel co-cultures (CD34+ cells with BMSCs) as measured by flow cytometry (n=3-14 chips or 3-9 wells per timepoint; data pooled from 5 independent experiments; # and & indicate P<0.05 at the indicated timepoints for static gel and suspension cultures, respectively, compared to BM Chips). h, Cell proliferation among total and CD34+ cells in BM Chips assessed by a 2-hour EdU pulse immediately prior to cell harvesting at the indicated timepoints (n=3-9 chips per timepoint; data pooled from 3 independent experiments; two-tailed Student’s t-test for % EdU+ cells among CD34+ versus total cells). (*P<0.05; **P<0.01; ***P<0.001).
**Supplementary Fig. 2** | a, Graphs showing total, myeloid, and erythroid cell numbers (top) within individual hematopoietic channels or combined from 3-4 vascular channels of BM Chips as measured by flow cytometry after 2 weeks of culture, as well as the percentage of neutrophils with a mature CD16<sup>hi</sup> surface phenotype (middle) and representative flow plots (bottom) showing neutrophil maturation status (hematopoietic channel, n=10 chips; vascular channel, n=3 pooled from 3 or 4 chips each; data pooled from 3 independent experiments). b, Schematic showing location of oxygen sensors in the modified BM Chip (top), 96 well static gel co-culture (middle) and suspension culture (bottom) setups. Graph at bottom shows oxygen levels (normalized to atmospheric levels) that were optically measured in the three culture setups on a daily basis for 2 weeks (n=3 measurements in one BM Chip, n=1 well in the static gel and suspension culture conditions).
Supplementary Fig. 3 | a, BM Chips, suspension cultures, and static gel co-cultures were matured for 10-12 days and treated for 48 hours with various doses of 5-FU. Cells were then harvested and analyzed by flow cytometry to quantitate erythroid cells (n=3-9 BM Chips or wells per concentration, data pooled from 3 independent experiments; *P<0.05; **P<0.01; ***P<0.001 for comparisons of BM Chips against both suspension and static gel cultures). b, Suspension cultures were matured for 10-12 days and then treated for 2 days with 5-FU before cells were harvested for analysis (gray). Alternatively, suspension cultures were continuously treated for 14 days (blue) to match overexposures in prior CFU-based studies. Total (left) and neutrophil lineage (right) cells were quantified by flow cytometry (n=3-9 wells per concentration except n=2 for the 14 day treatment at 40µM; data pooled from 2 independent experiments). c, Suspension cultures were treated with 5-FU using the clinically relevant regimen of 4µM for 48 hrs on the indicated days. Cells were harvested on day 12 (for day 10 treated cultures) or day 14 (all other cultures) and analyzed by flow cytometry. (n=6-14 wells per condition; data pooled from 3 independent experiments; ***P<0.001 for drug-treated versus control cultures). d, Results of PK models of BM Chip drug exposure (lines) derived from the measured drug concentrations for BM Chips (circles) that were matured for 10 days, treated with 2-hour or 48-hour infusions of AZD2811 (total AUC of 0.5µM.h, 1µM.h, and 2µM.h), and then cultured again in drug-free medium compared with an average patient's plasma values that were simulated at a range of clinical doses based upon the known PK characteristics of AZD2811 (Pt plasma). Dotted line represents the detection limit of mass spectrometry during these experiments. AZD2811 concentrations were measured by mass spectrometry in BM Chip outlet medium collected at various timepoints during and after drug infusion (ND = not detectable). e, BM Chips were matured for 10 days and treated with various exposures of AZD2811 for 2 hours (left) versus 48 hours (right). Total cell numbers were quantified on day 12 by flow cytometry. (n=5-6 chips per condition; data pooled from 2 independent experiments; two-tailed Student’s t-test for drug-treated versus control BM Chips; *P<0.05; **P<0.01; ***P<0.001).
Supplementary Fig. 4 | a, Incidence of severe neutropenia previously reported in patients receiving 2-hour or 48-hour infusions of AZD2811 administered as barasertib every 2 weeks\textsuperscript{35,37}. X-axis refers to free AUC (4% of total in human plasma; 37.5% of total in BM Chip medium). Labels: # of neutropenic pts/# of total pts at each dose. b, BM Chips were matured for 10 days and treated with various exposures of AZD2811 for 2 hours (left) versus 48 hours (right). Immature CD16lo and mature CD16hi neutrophils were quantified on day 12 by flow cytometry. (n=5-6 chips per condition; data pooled from 2 independent experiments; two-tailed Student's \textit{t}-test for drug-treated versus control BM Chips; *P<0.05; **P<0.01; ***P<0.001). c, Hematologic side effects previously reported in patients receiving 2-hour or 48-hour infusions of similar total exposures to AZD2811 administered as barasertib\textsuperscript{32,34} (top). Suspension cultures were matured for 10 days and then treated with the same total exposures to AZD2811 administered over 2 hours (left) versus 48 hours (right). Cells were harvested on day 12 and neutrophils (blue) and erythroid (red) cells were quantified by flow cytometry (bottom). (n=6 wells per condition; data pooled from 2 independent experiments; two-tailed Student's \textit{t}-test for drug-treated versus control cultures; ***P<0.001).
Supplementary Fig. 5 | a, Total (left) and CD34+ (right) cell numbers in BM Chips that were matured for 10 days, irradiated with 0, 1, 2 or 4 Gy, and sacrificed at day 14 (n=3 chips, data representative of 2 independent experiments). b, BM Chips were created using CD34+ progenitor cells from 5 different donors (each color represents an individual donor; n=3-4 replicates per patient) and treated with varying doses of radiation after 10-12 days of maturation. Total (left) and CD34+ (right; log scale y-axis) cell numbers were quantified at day 14. c, Suspension cultures were treated on day 10 with the highest total exposure of AZD2811 (2µM.h) over 2 or 48 hours and subsequently allowed to recover in drug-free medium until day 19. CD34+ cell numbers (left) were minimally affected when quantified at day 12. Neutrophil numbers (right) were quantified by flow cytometry at days 10, 12, and 19 to assess the ability of suspension cultures to recover after injury (n=6 chips per condition at each timepoint; data pooled from 2 independent experiments; two-tailed Student’s t-test for drug-treated versus control cultures). **P<0.01; ***P<0.001.
| Patient | SBDS mutation                                         | Karyotype   |
|---------|-------------------------------------------------------|-------------|
| 1       | Homozygous c.258+2T>C                                  | 46XY [normal] |
| 2       | c.183_184delTAinsCT and c.258+2T>C                    | 46XY [normal] |

**Supplementary Fig. 6** | a, SBDS mutation characteristics and karyotype of the two SDS patients from whom cells were cultured in BM Chips. b, BM Chips containing normal or SDS CD34+ cells were matured for 14 days. Numbers of total cells (b) and immature CD16lo vs mature CD16hi neutrophils (c) were quantified by flow cytometry (n=8; pooled from 2 independent experiments, each using cells from a different normal and SDS patient with 4 chips per experiment; two-tailed Student’s t-test for SDS versus normal BM Chips; **P<0.01; ***P<0.001).
Supplementary Fig. 7 | Representative flow cytometry gating scheme to quantify total, CD34+, neutrophil lineage, and erythroid lineage cells.
**Summary of 3D and dynamic human hematopoietic culture models**

| BM model | Disease modeling | Additional applications |
|----------|-----------------|------------------------|
|          |                 |                        |
| Gel      | Non-neoplastic  | Progenitor expansion   |
|          | Genetic         |                        |
|          | Rad/Drug injury |                        |
|          | AML, MM         |                        |
| Scaffold | No              | Progenitor expansion   |
|          | No              |                        |
|          | AML, CML, MM    |                        |
| Bioreactor | No          | Platelet production   |
|          | Bleomycin       |                        |
|          | 5-fluouracil    |                        |
|          | PMF             |                        |
| Microfluidic | No            | Platelet production   |
|          | No              |                        |
|          | ALL, MM         |                        |
| Other    | No              | Progenitor expansion   |
|          | No              |                        |
|          | MM              |                        |

ALL = acute lymphoblastic leukemia, AML = acute myeloid leukemia, CML = chronic myelogenous leukemia, MM = multiple myeloma, PMF = primary myelofibrosis

*Model definitions:
Gel = solid gels lacking a macroporous design
Scaffold = soft and hard 3D structures with a macroporous design
Bioreactor = perfused macro-scale device
Microfluidic = perfused micro-scale device
Other = automated medium dilution setup on orbital shaker, spinner flasks, rotating devices, and miscellaneous other systems

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