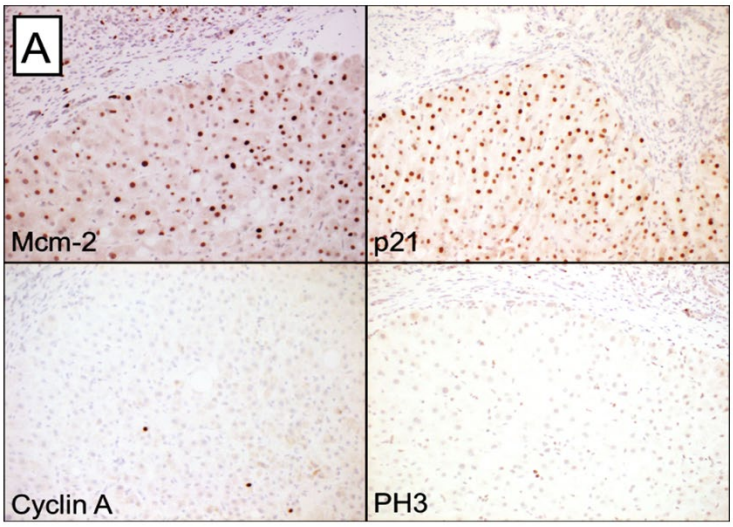
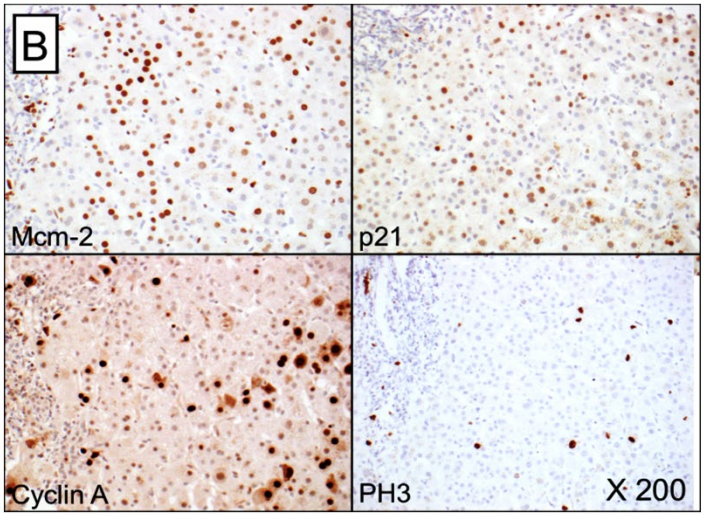
Supplementary figure 1a.



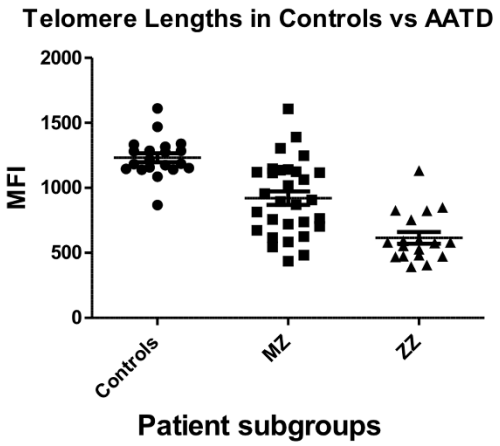
Supplementary figure 1a. Representative images of a liver section from a patient with cirrhosis. The edge of the same portal tract is shown in every image. Note frequent positive hepatocyte nuclear staining with both Mcm-2 and p21. Few or no hepatocytes expressed cyclin A or PH3. A few inflammatory cells have also stained positive for cyclin A and PH3 in this section and thus serve as an internal positive control.

Supplementary figure 1b.



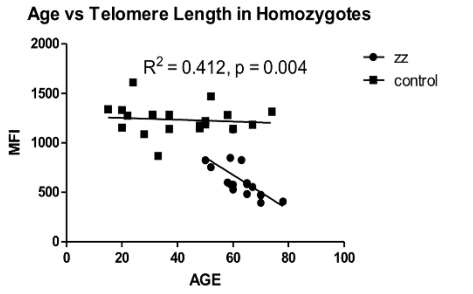
Supplementary figure 1b. For comparison with supplementary figure 1a, a liver section from a patient with regeneration after ischaemia-reperfusion injury. The edge of the same portal tract is shown in each image. Note positive hepatocyte nuclear staining with all four markers, with the highest proportion of positive cells for Mcm-2, then p21, cyclin A and PH3.

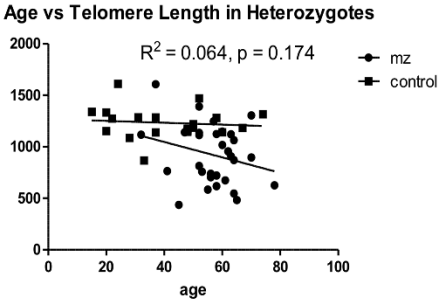
Supplementary figure 2a



Supplementary figure 2a. Hepatocyte telomere lengths, expressed as mean fluorescent intensity (MFI), were reduced in patients with α_1-antitrypsin deficiency, an effect that was more marked in those homozygous for the Z allele compared with those heterozygous for the Z allele.

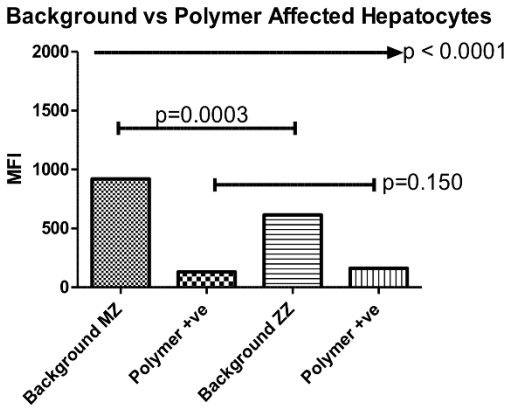
Supplementary figure 2b





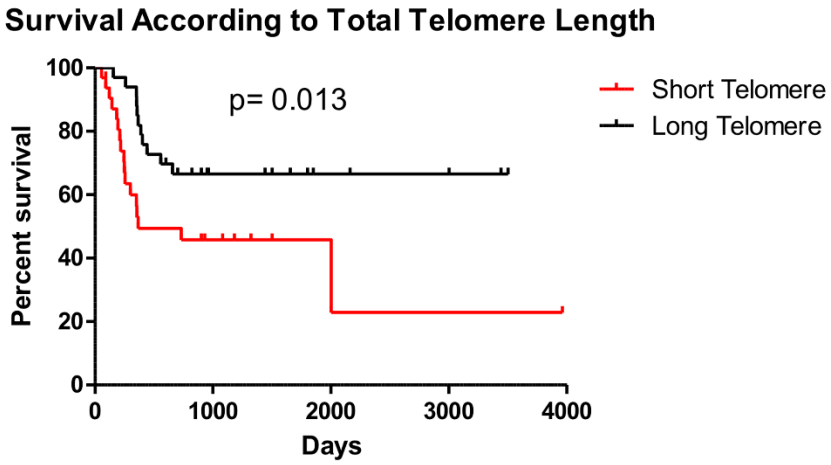
Supplementary figure 2b. Hepatocyte telomere lengths remain constant in healthy individuals with time but fall progressively with increasing age in patients with α_1-antitrypsin deficiency. The rate of loss of telomere length with age was greater in those homozygous for the Z allele (top panel) when compared with those heterozygous for the Z allele (bottom panel).

Supplementary figure 2c.



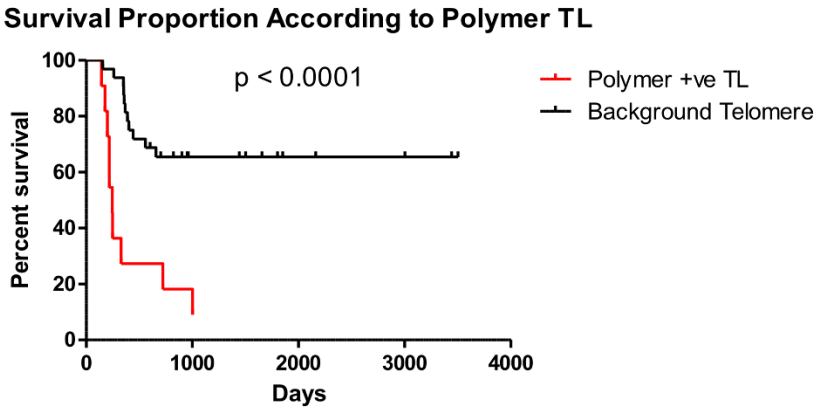
Supplementary figure 2c. Median hepatocyte telomere lengths measured in α_1-antitrypsin polymer positive hepatocytes compared with α_1-antitrypsin polymer negative hepatocytes in liver sections from patients with either homozygous or heterozygous α_1-antitrypsin deficiency, suggesting a direct effect of the polymer on reduced telomere length.

Supplementary figure 2d



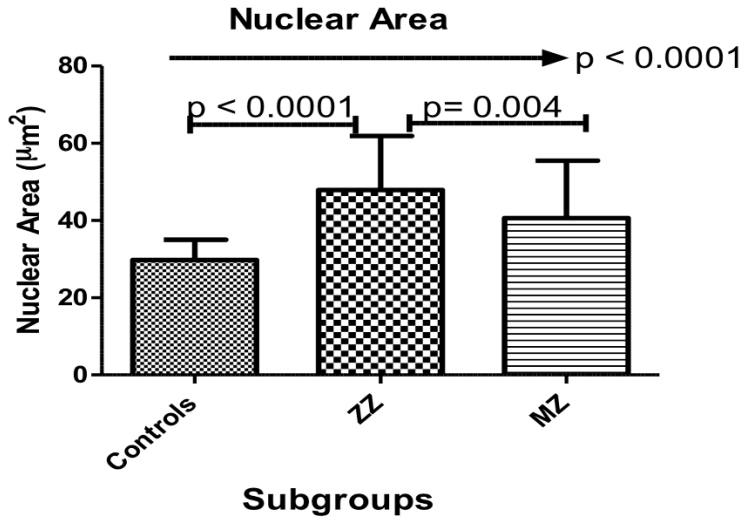
Supplementary figure 2d. Patients in whom the hepatocyte telomere length was below the median have an increased risk of liver-related mortality (red line) compared to those in whom the hepatocyte telomere length was above the median (black line).

Supplementary figure 2e



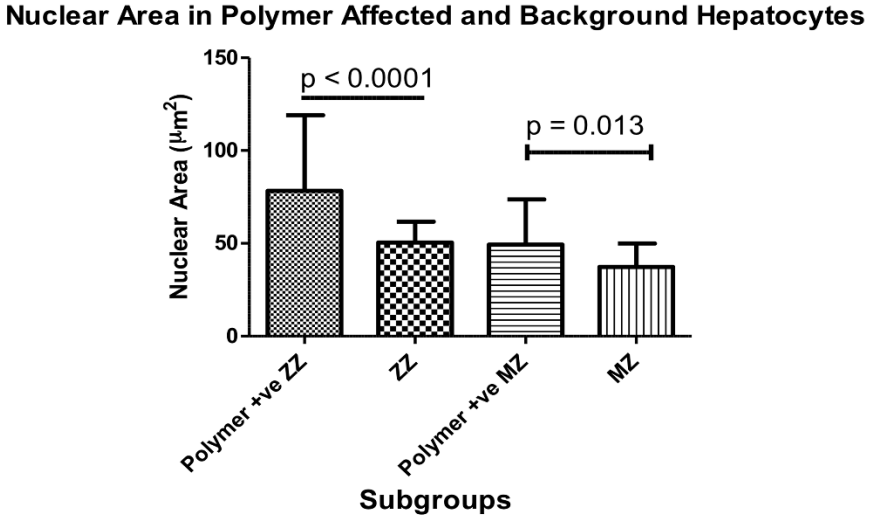
Supplementary figure 2e. The effect of hepatocyte telomere length on liver-related mortality was even more marked when only those hepatocytes expressing α_1-antitrypsin polymers were analysed. Those with hepatocytes that expressed α_1-antitrypsin polymers with telomeres shorter than the median had increased liver related mortality (red line) compared to those with telomeres longer than the median (black line).

Supplementary figure 3a



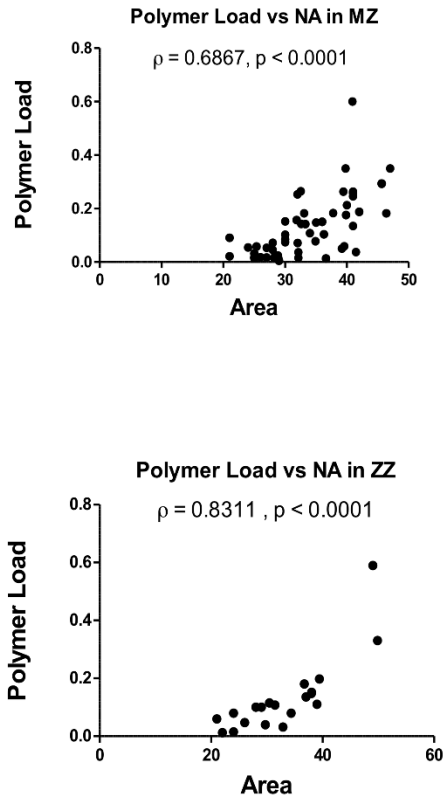
Supplementary figure 3a. Hepatocyte nuclear area increases in cellular senescence and was greater in patients with α_1-antitrypsin deficiency when compared with controls, an effect that was more marked in those homozygous for the Z allele when compared with those heterozygous for the Z allele.

Supplementary figure 3b



Supplementary figure 3b. Hepatocyte nuclear area was greater in patients with α_1-antitrypsin deficiency within hepatocytes that expressed polymers when compared to hepatocytes in the same patients that did not express the polymer, again an effect that was more marked in those homozygous for the Z allele when compared with those heterozygous for the Z allele.

Supplementary figure 3c



Supplementary figure 3c. Hepatocyte nuclear area increased in parallel with α_1-antitrypsin polymer load in patients α_1-antitrypsin deficiency, an effect that again was more marked in those homozygous for the Z allele (bottom panel) when compared with those heterozygous for the Z allele (top panel).