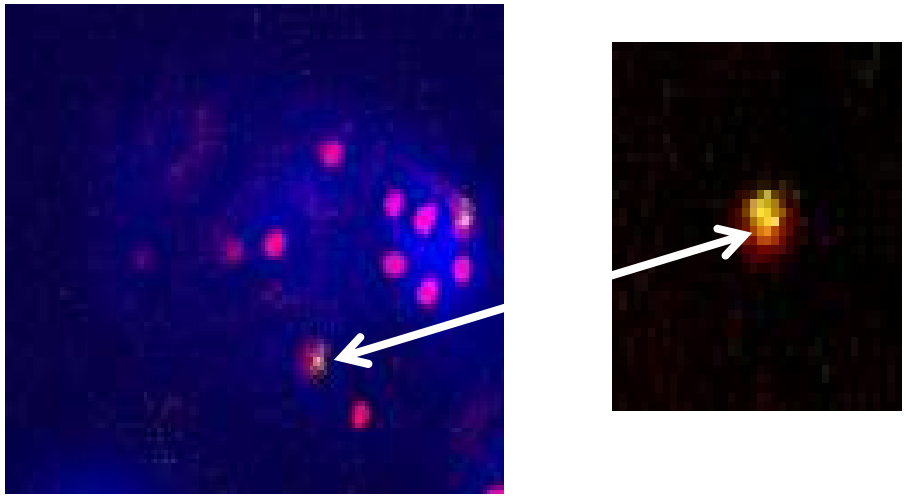
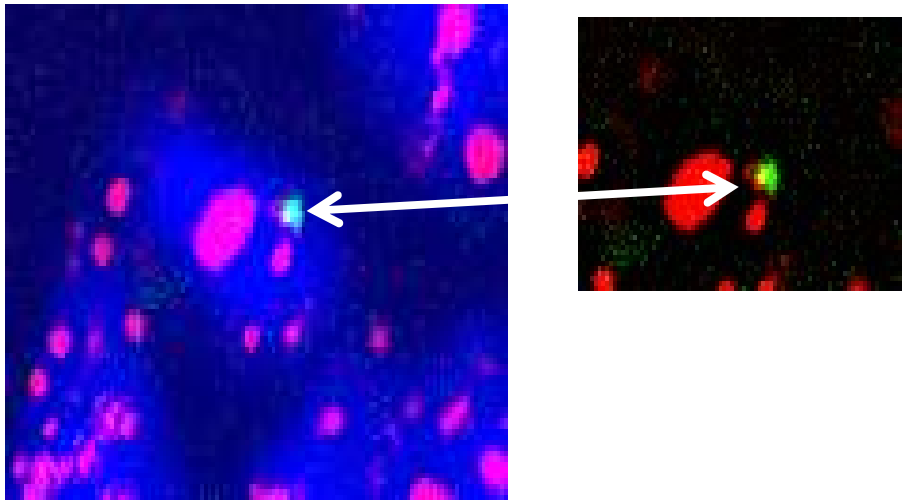
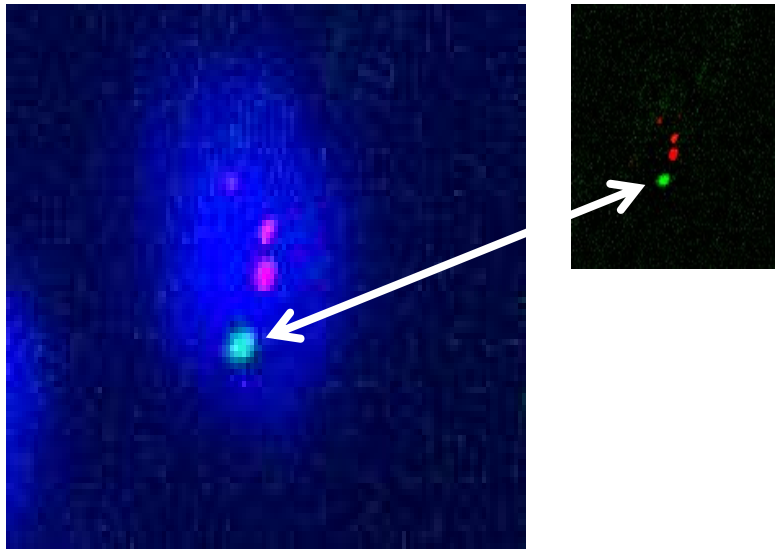


(a)



(b)



(c)

Figure ??: Typical positive telomere co-localisation of 53BP with telomeres in (a) lung wt at 700days, (b) lung *IRS1* $^{-\backslash-}$ at 700days and (c) typical TIF negative showing presence of both 53BP and telomeres but not co-localised.

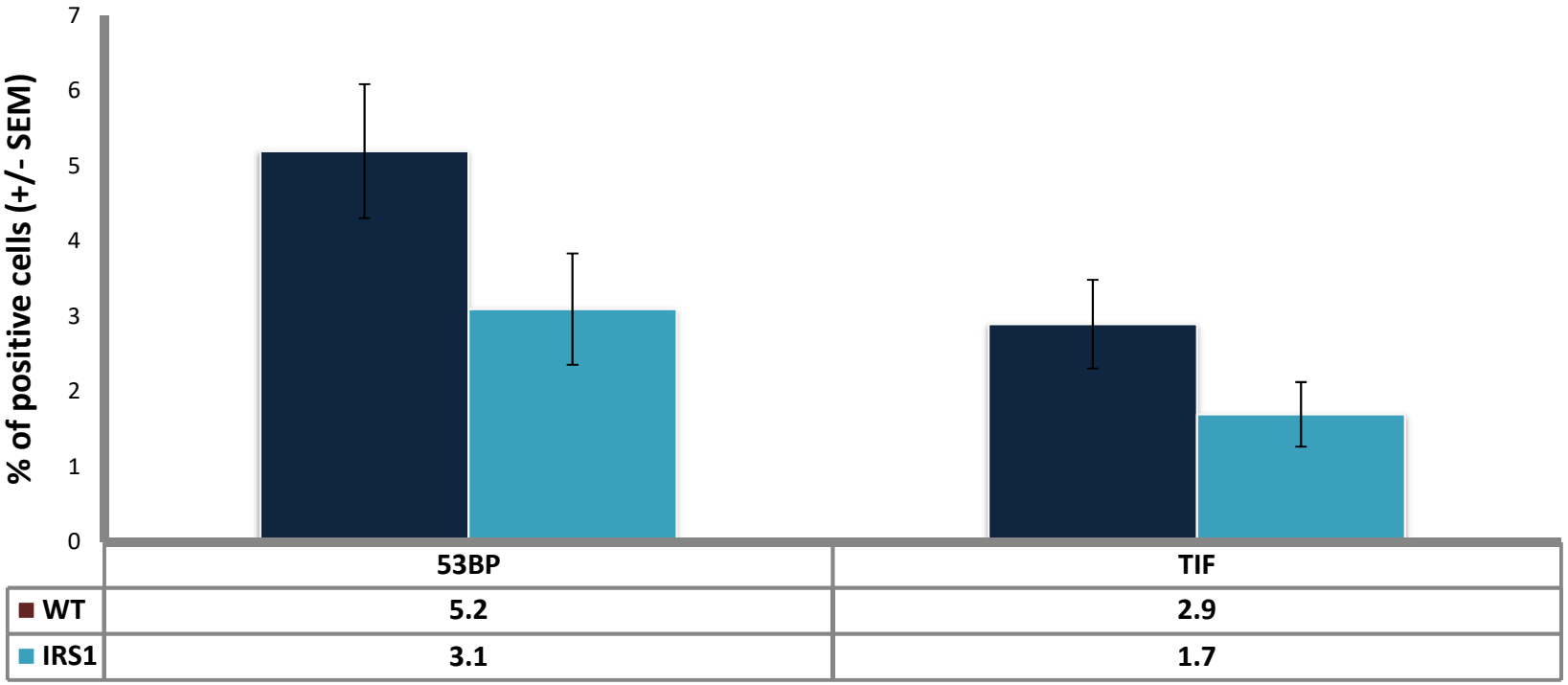


Figure ??: Telomere dysfunction in lung tissue between 700 day old WT and *Irs1* $^{-/-}$ C57/B6 mice.

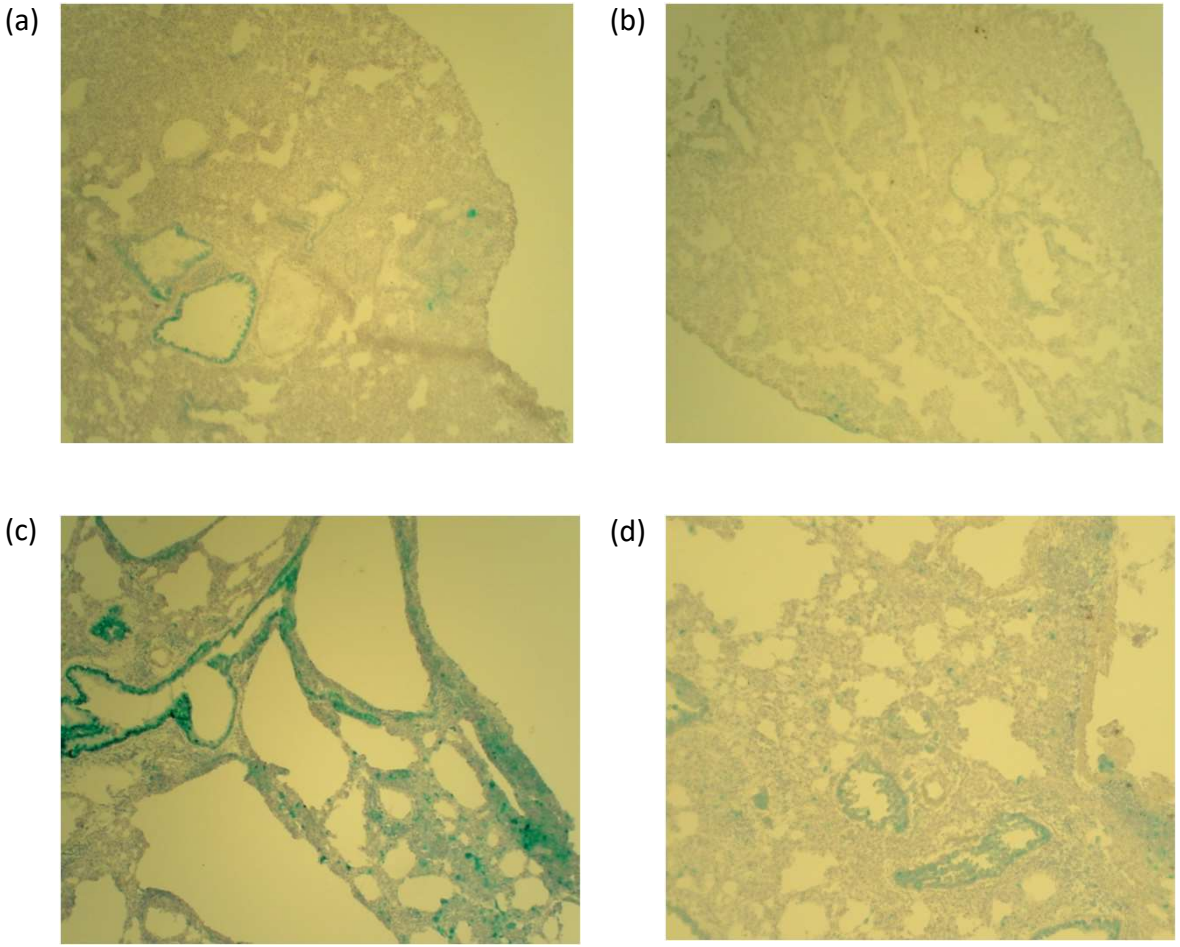


Figure ??: Senescent associated β-galactosidase (SA-β-Gal) assay on lung tissue at pH 6 at (a) Wt 80-90days, (b) IRS1$^{-/-}$ 80-90days, (c) Wt 700 days and (d) IRS1$^{-/-}$ 700days. Typical positive staining giving rise to a blue precipitate in the cytosol.

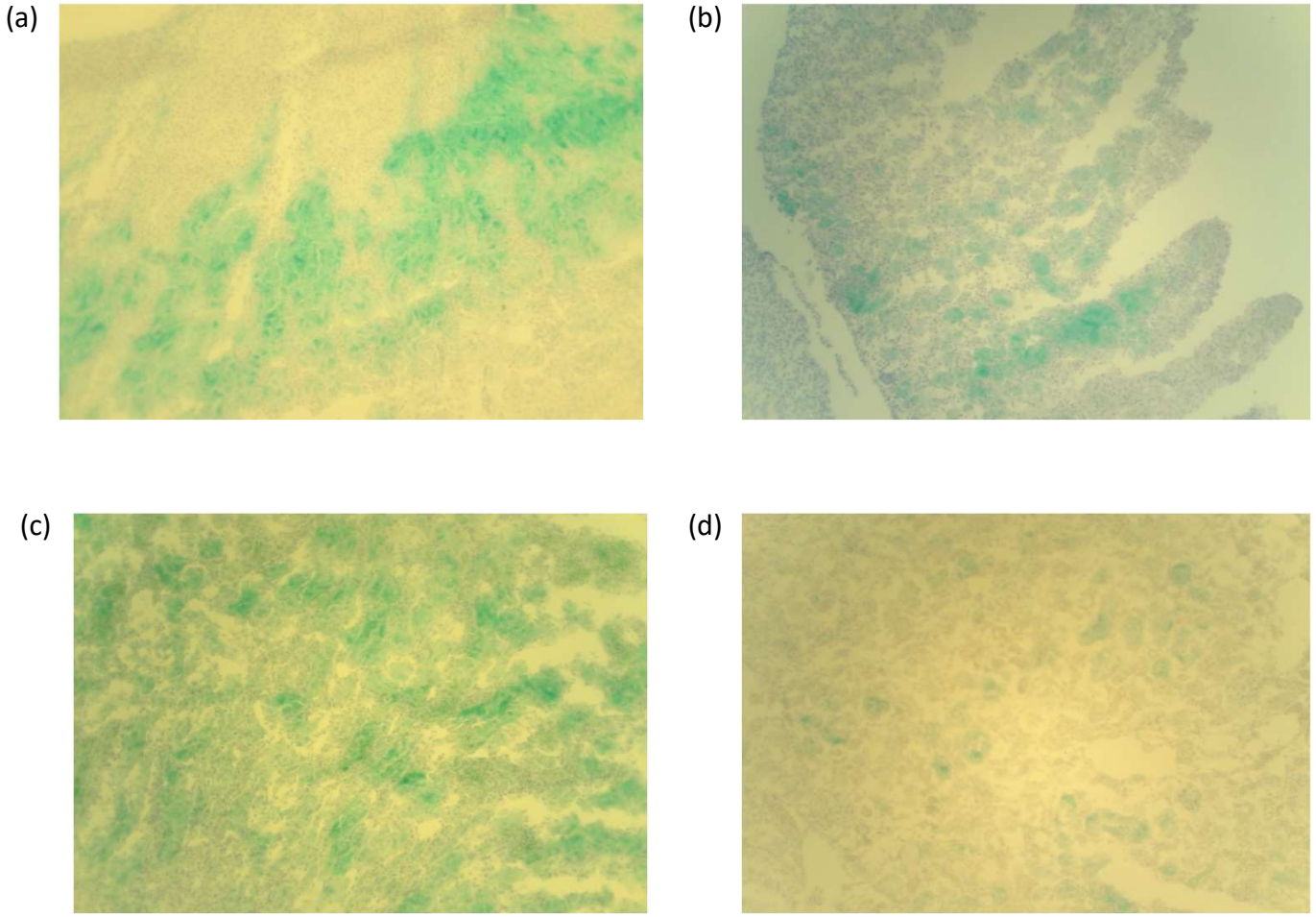


Figure ??: Senescent associated β-galactosidase (SA-β-Gal) assay on kidney tissue at pH 6 at (a) Wt 80-90days, (b) $IRS1^{-/-}$ 80-90days, (c) Wt 700 days and (d) $IRS1^{-/-}$ 700days. Typical positive staining giving rise to a blue precipitate in the cytosol.

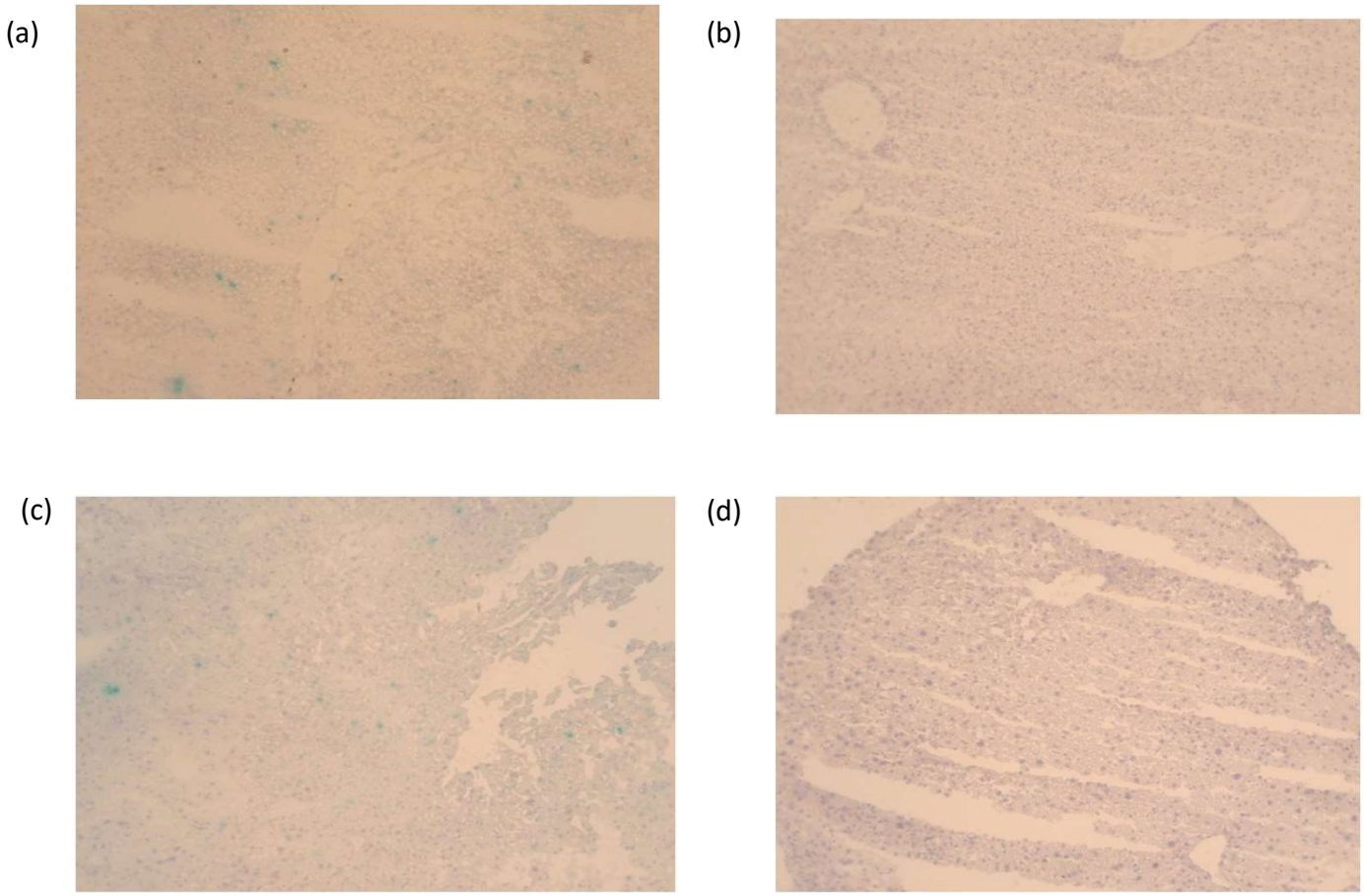


Figure ??: Senescent associated β-galactosidase (SA-β-Gal) assay on liver tissue at pH 6 at (a) Wt 80-90days, (b) $IRS1^{-/-}$ 80-90days, (c) Wt 700 days and (d) $IRS1^{-/-}$ 700days. Typical positive staining giving rise to a blue precipitate in the cytosol.

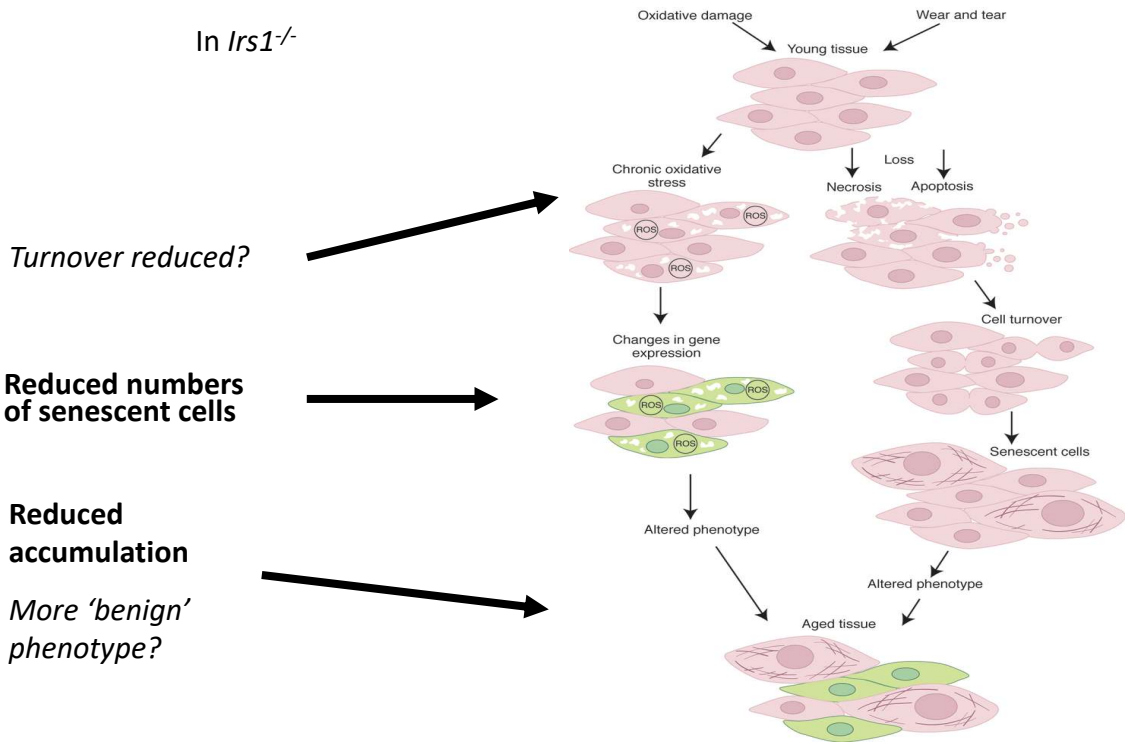


Figure ??: *Simplified diagram illustrating the relationship between cell senescence and tissue ageing* in *Irs1*$^{-/-}$ mice. ***Right hand flow diagram:*** *Cell loss in mitotic tissues is balanced by cell division. Cell division is actively monitored as an anti-cancer mechanism triggering exit from the cell cycle via a variety of molecular mechanisms. Senescent cells have a dramatically altered phenotype that adversely affects tissues in which they accumulate.* ***Left hand flow diagram****: chronic oxidative stress or excess mitogenic signalling can also induced irreversible cells cycle exit and the generation of senescent cells.*

Tissue type	Wt Vs IRS1$^{-/-}$ (80-90 days)	Wt Vs IRS1$^{-/-}$ (450 days)	Wt Vs IRS1$^{-/-}$(700 days)	Embedded for Cryostat	Frozen for RNA/Protein work	Embedded for wax	Primary cultures established
Brain	2 Vs 2	4 Vs 3	3 Vs 4	√	√	-	-
Kidney	**2 Vs 2**	**4 Vs 3**	**3 Vs 4**	√	√	**-**	**-**
Liver	**2 Vs 2**	**4 Vs 3**	**3 Vs 4**	√	√	**-**	**-**
Skin	2 Vs 2	4 Vs 3	3 Vs 4	√	-	-	√
Lung	**2 Vs 2**	**4 Vs 3**	**3 Vs 4**	√	**-**	**-**	√
Ear	-	4 Vs 3	3 Vs 4	-			√
Heart	2 Vs 2	4 Vs 3	3 Vs 4	√	-	√	-
Great vessels	2 Vs 2	4 Vs 3	3 Vs 4	-	-	√	-

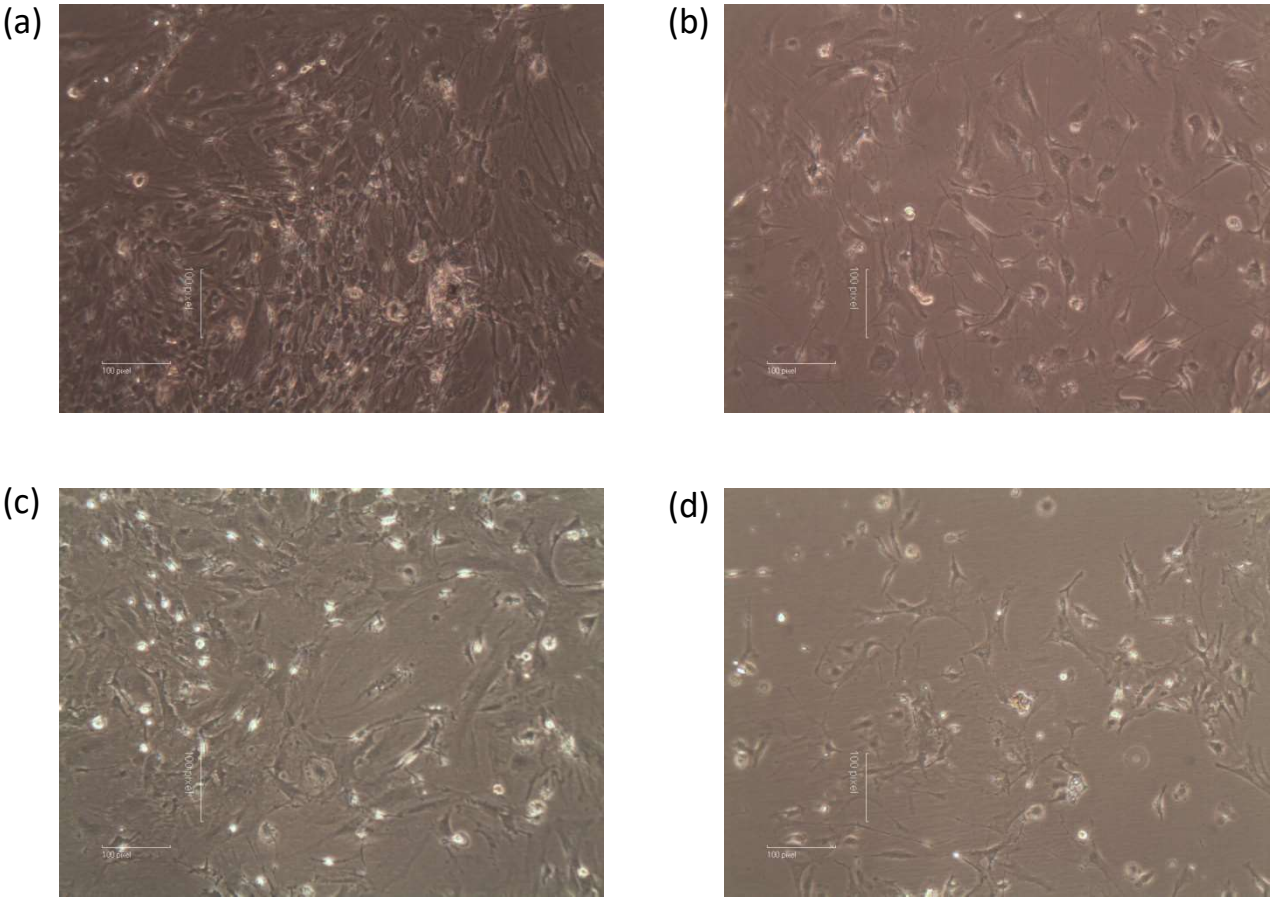


Figure 1: Typical cultures established from wt and IRS1$^{-\backslash-}$ animals at 80-90 day (a) wt skin at passage 1, (b) IRS1$^{-\backslash-}$ skin at passage 1, (c) wt lung at passage 1 and (d) IRS1$^{-\backslash-}$ lung at passage 1.

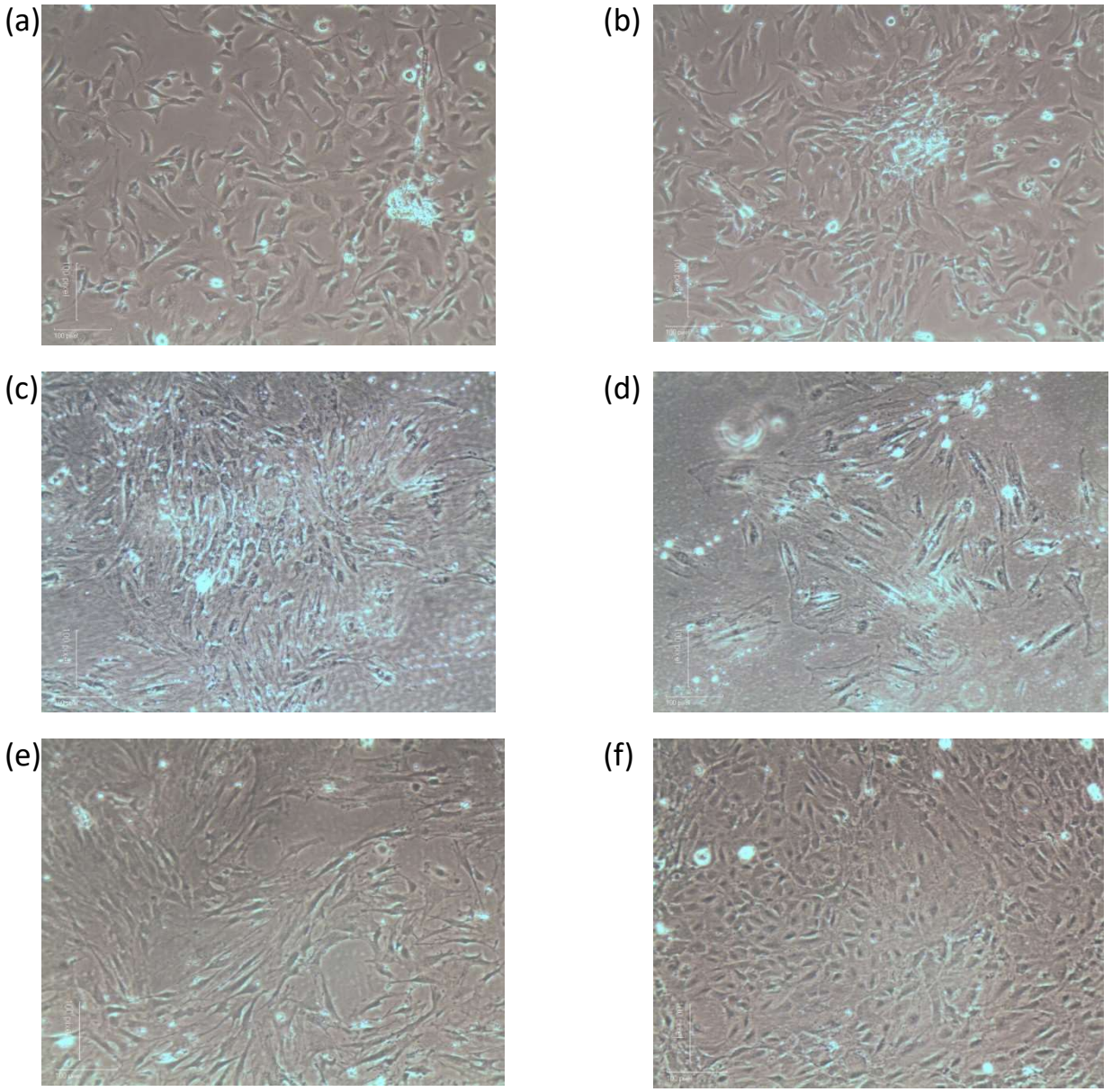


Figure 2: Typical cultures established from wt and IRS1$^{-\backslash-}$ animals at 7000 day (a) wt ear at passage 0, (b) IRS1$^{-\backslash-}$ ear at passage 0, (c) wt skin at passage 0, (d) IRS1$^{-\backslash-}$ skin at passage 0, (e) wt lung at passage 0 and (f) IRS1$^{-\backslash-}$ lung at passage 0.