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Cystinosis and Mickey Mouse

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What could the knockout mouse and Mickey Mouse possibly have in common? They appear as polar opposites. One inhabits a laboratory, scorned for the latest failed experiment. The other, more at home in the glitz of Hollywood, is adored by all [1]. Aside from the ears though, the

similarities are profound, whereas Mickey serves as the comic-everyman, the knockout mouse enjoys the dubious honour of being every man's (or woman's) genetic stand-in.

Cystinosis, like Mickey Mouse, is known to all paediatric nephrologists, less so to those specializing in adults.

It was first diagnosed over a century ago in children exhibiting a failure to thrive, leading to premature death. It was subsequently recognized as a cystine-related lysosomal storage disorder [2]. Untreated patients present in infancy first with renal Fanconi syndrome and then, at about 10 years of age, suffer glomerular kidney failure necessitating renal replacement therapy [3]. Following the cloning of the gene, CTNS, 10 years ago, molecular studies have proved patients affected with this problem are present all over the world. Years before, smart biochemists had discovered a specific treatment—cysteamine [4]. Clinical trials and treatment over the past 40 years have proved without doubt that this treatment helps. In fact, it helps a lot [5]. Contrast this with as recently as the 1960s, when patients would still have died during childhood. Nowadays, they can expect to live into their fifties at the very least [6], illustrating the importance of medical doctors and nephrologists of all stripes being able to diagnose and treat this condition.

Advances in biomedical science have made genetically modified mice readily available. Since their conception by Oliver Smithies and colleagues, the study of knockout mice has almost become a science in its own right [7].

Studying knockout mice, like human patients, takes time, dedication and expert knowledge. Cloning a gene and creating a knockout mouse as proof of principle still counts as a major accomplishment in medical research today. Dr. Antignac's group not only cloned the gene [8], but also created the first knockout mouse for cystinosis [9]. Unfortunately, this particular mouse did not show what was expected. Despite biochemical measurements pointing towards cystine-related lysosomal storage, no signs or symptoms of kidney failure of either tubular or glomerular origin could be appreciated. Quite a shame; imagine Mickey Mouse, but without the laughter!

Undeterred, Dr. Antignac and her team revisited the issue, creating another knockout mouse and, like all good mice thrown into the spotlight, this one did not disappoint. Their new mouse shows kidney involvement [10].

What went wrong the first time? We believe it was no fault of the method. We must appreciate the depth of some mice to be greater than the comic spills of cartoon characters. It turns out that knockout mice are not as simple as we once thought. Life is complicated enough and knocking out a gene does not always create reproducible and unique phenotypes. Much like patients within the same family with variations of the same monogenetic disease, the mice can be quite different from each other. Knockout mice

have been bred for a purpose, using inbred mouse strains, from all over the world for many years. This can translate into actually having many biased gene functions. In this case, the first knockout mouse created for cystinosis on the genetic background of 129Sv and C57BL/6 probably had some genes functioning in a protective manner in comparison to the new knockout mouse created on the background of C57BL/6 mice. Additionally, having FVB/N mice as background for this knockout produced no kidney findings whatsoever. It would be quite nice to compare genomes of the three mouse strains to better understand their differences and potentially help explain protection against kidney disease.

Dr. Antignac's group has created another mouse to play foil to man, who will certainly help improve our understanding, specifically, of cystinosis and, broadly, of kidney disease. We welcome this new mouse in our community.

Conflict of interest statement. None declared.

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