Come together, right now....

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Abstract Editing the genome using approaches like TALEN and siRNA are already well tested. The new kid on the block is CRISPR-Cas9. CRISPR-Cas9 is rapidly evolving with impressive refinements for specificity, eliminating off-target effects, and versatility. One can adjust constructs and conditions to produce opposite effects on the genome and for a specific purpose. The nuances of the system, the means to significantly reduce off-targeting, and numerous applications are now emerging rapidly. This B&B commentary looks forward into how the CRISPR-Cas9 tool might serve the CCN field.

Keywords Genome editing · CRISPR-Cas9 · Correcting human disease · CCN applications

Just when you thought you had a good grasp of next generation sequencing (NGS), RNA-seq, and iPSC along comes the explosive (>1000 publications in the recent 2 years) method of genome editing using the CRISPR-Cas9 system.

Essentially the acronym stands for ‘Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)/Cas9: an RNA guided DNA endonuclease’ stems from some elegant work in bacteria, on prokaryotic adaptive immunity against viruses, but was quickly recognized as a highly promising method to perform programming manipulations in eukaryotic organisms via a specific guide RNA (sgRNA). DNA double strand breaks are catalyzed by Cas9 and repair via intrinsic error-prone NHEJ permits further molecular manipulations.

So what is this miracle tool? Editing the genome is not really new and other approaches like TALEN and siRNA are already well tested and can now be compared with CRISPR-Cas9 for their usefulness and applications (Boettcher and McManus 2015). CRISPR-Cas9 is also rapidly evolving as does every molecular tool that needs refinement for specificity, eliminating off-target effects, and versatility (Boettcher and McManus 2015; Nihongaki et al. 2015). One can adjust constructs and conditions to produce opposite effects on the genome and for a specific purpose. The nuances of the system, the means to significantly reduce off-targeting, and numerous applications are now emerging rapidly (Stenberg and Doudna 2015; Hecki and Charpentier 2015; Moore 2015; Hartenian and Doench 2015; Gilles and Averof 2015; Yan et al. 2014; Harrison et al. 2014). Design of the sgRNA is critical and can greatly enhance the specificity.

Praises are being sung by leading scientists, futurists, and in online newsletters who now see this as the route into curing genetic disease, doing what only science fiction writers could dream of, and all of this now rapidly transitioning into guaranteed kit forms and biotech services for laboratories. Here in my institute it has rapidly taken hold in the everyday vernacular and has almost achieved the equivalent to the ‘taken for granted’ approach of ‘we created a Cre-lox ...etc....mouse’, routine, no? Costs are coming down and who knows, maybe, it will become the preferred Christmas present for that budding scientist in your family who wants to be ‘creative’.

So how has the CCN field and its investigators taken to this new technology? Thus far little has been published, going by the current literature, however, I am certain it is already bubbling away in the labs or slated within future plans. After all, would it not be exciting to be able to manipulate CCN transcription to determine how an absolute deletion or insertion of a specific CCN protein(s) could alter phenotypes and functions.

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Given the complex nature of the matricellular environment and contributions of matricellular CCN proteins (Murphy-Ullrich and Sage 2014; Bedore et al. 2014) a total deletion or insertion of one and more CCN proteins could reveal yet unknown functions for these proteins.

So now, let's do a little matchmaking. The ability to induce development of every cell phenotype from iPSC cells, reprogrammed from simple fibroblasts (and other cell types as well) and proven applicable for human normal and disease conditions (Corti et al. 2015; Yang et al. 2015; Li et al. 2014; Curry et al. 2015), offers an opportunity to delete or insert (as one type of manipulation) CCN expressions using CRISPR-Cas9 and reveal how CCN proteins contribute to normal development and affect disease phenotypes when iPSC undergo induced differentiation. You can then imagine how further analyses will evolve. We know a lot more about the roles of CCN2 (Kubota and Takigawa 2015; Aguiar et al. 2014; Wells et al. 2015) but this approach might now offer opportunities to probe the entire CCN family in a single developmental context (Ishihara et al. 2014).

Is there a precedent? New exciting developments using the CRISPR-Cas9 method to potentially correct diseases (Humphrey and Kasinski 2015) like muscular dystrophy (Ousterout et al. 2015) and hematopoietic diseases (Song et al. 2015) set the stage for an expected coming deluge of papers on many other syndromes as proof-of-principle.

From a personal point of view, many older investigators, like myself, might look back at the CCN studies of the 1980s and when comparing with today, view these older studies as uncovering artifacts in a dig. Every part of biomedical research is now moving along at breakneck speed. It is becoming more difficult not just to stay current but actually hold on. It definitely behooves CCN investigators to form team collaborations for the research momentum needed for the future.

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