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Generation of anti-Progranulin camelid nanobodies

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Background: Progranulin (PGRN) haploinsufficiency is a common genetic cause of Frontotemporal Dementia. PGRN is processed into granulins, which are thought to regulate lysosomal homeostasis. The lack of specific antibodies against PGRN and individual granulins has slowed efforts to understand their function and binding partners. The development of recombinant antibodies against PGRN would be essential tools to help answer these important questions. Moreover, single-domain variable heavy-chain antibodies (VHHs), commonly called nanobodies, have unique properties that make them excellent research tools compared to conventional monoclonal antibodies. Nanobodies are small (~15 kDa), recognize unique epitopes, have high affinities, and can be produced inexpensively. Here, we developed PGRN nanobodies to further investigate the abundance and function of PGRN and granulins.
Methodology: Purified human N-TAP PGRN was used to immunize a llama and generate a recombinant phage-displayed camelid VHH library, which was screened against PGRN to isolate potential candidate binding nanobodies.
Results: We identified 37 unique clones that expressed soluble VHHs which selectively bound PGRN. From this pool, we selected 7 nanobodies with different complementary determining regions (CDRs) to further characterize. Nanobodies detected endogenous PGRN, and selectivity was verified using multiple methods including *GRN*-/- cells. Precise mapping of nanobody epitopes is ongoing. Furthermore, anti-PGRN nanobodies successfully co-immunoprecipitated PGRN from media and cells. Computational modeling of PGRN nanobodies with antigens will provide structural insight into antigen-binding sites and epitope selectivity.
Conclusion: We have successfully generated PGRN-specific nanobodies, which have multiple applications including basic science, structural biology, diagnostics, and therapeutics.

Conflicts of interest

N/A