Supplementary Table 1. Published IgNARV binders to target antigens.

Target	Potential Application	Source	Species	Reference
IL-8	Anti-inflammation	?	?	[1]
HBeAg of HBV	Anti-viral	Semi-synthetic	Wobbegong	[2]
Viral hemorrhagic septicemia virus	Anti-viral	Semi-synthetic	Banded houndshark	[3]
HTRA1	Arthritis therapy	Semi-synthetic	Bamboo shark	[4]
Cholera toxin	Biosensor	Naïve	Spiny dogfish	[5]
EpCAM	Cancer diagnostic & therapy	Semi-synthetic	Bamboo shark	[4]
EphA2	Cancer diagnostic & therapy	Semi-synthetic	Bamboo shark	[4]
Tom70	Diagnosis and therapy	Semi-synthetic	Wobbegong	[6]
TNF-α	Endotoxic shock	Immunized	Horn shark	[7]
HSA	Half-life extension	Immunized	Spiny dogfish	[8]
Ebola virus	Immunodiagnostic	Immunized	Nurse shark	[9]
Gingipain K protease	Proof of concept	Naïve/semi-synthetic	Wobbegong	[10,11]
HEL	Proof of concept	Immunized	Nurse shark	[12]
HEL	Proof of concept	Semi-synthetic	Banded houndshark	[13]
Leptin	Proof of concept	Semi-synthetic	Nurse shark	[14]
AMA1	Malaria diagnosis	Semi-synthetic	Wobbegong	[15,16]
Staphylococcal enterotoxin B	Sensor	Semi-synthetic	Spiny dogfish	[17]
Ricin	Sensor	Semi-synthetic	Spiny dogfish	[17]
Botulinum toxin	Sensor	Semi-synthetic	Spiny dogfish	[17]

Supplementary References

1. Zielonka S, Empting M, Grzeschik J, Konning D, Barelle CJ, Kolmar H: **Structural insights and biomedical potential of ignar scaffolds from sharks.** *mAbs* (2015) **7**(1):15-25.

2. Walsh R, Nuttall S, Revill P, Colledge D, Cabuang L, Soppe S, Dolezal O, Griffiths K, Bartholomeusz A, Locarnini S: **Targeting the hepatitis b virus precore antigen with a novel ignar single variable domain intrabody.** *Virology* (2011) **411**(1):132-141.

3. Ohtani M, Hikima J, Jung TS, Kondo H, Hirono I, Takeyama H, Aoki T: **Variable domain antibodies specific for viral hemorrhagic septicemia virus (vhsv) selected from a randomized ignar phage display library.** *Fish & shellfish immunology* (2013) **34**(2):724-728.

4. Zielonka S, Weber N, Becker S, Doerner A, Christmann A, Christmann C, Uth C, Fritz J, Schafer E, Steinmann B, Empting M *et al*: **Shark attack: High affinity binding proteins derived from shark vnar domains by stepwise in vitro affinity maturation.** *Journal of biotechnology* (2014) **191**(236-245.

5. Liu JL, Anderson GP, Delehanty JB, Baumann R, Hayhurst A, Goldman ER: **Selection of cholera toxin specific ignar single-domain antibodies from a naive shark library.** *Mol Immunol* (2007) **44**(7):1775-1783.

6. Nuttall SD, Krishnan UV, Doughty L, Pearson K, Ryan MT, Hoogenraad NJ, Hattarki M, Carmichael JA, Irving RA, Hudson PJ: **Isolation and characterization of an ignar variable domain specific for the human mitochondrial translocase receptor tom70.** *European journal of biochemistry / FEBS* (2003) **270**(17):3543-3554.

7. Bojalil R, Mata-Gonzalez MT, Sanchez-Munoz F, Yee Y, Argueta I, Bolanos L, Amezcua-Guerra LM, Camacho-Villegas TA, Sanchez-Castrejon E, Garcia-Ubbelohde WJ, Licea-Navarro AF *et al*: **Anti-tumor necrosis factor vnar single domains reduce lethality and regulate underlying inflammatory response in a murine model of endotoxic shock.** *BMC immunology* (2013) **14**(17.

8. Muller MR, Saunders K, Grace C, Jin M, Piche-Nicholas N, Steven J, O'Dwyer R, Wu L, Khetemenee L, Vugmeyster Y, Hickling TP *et al*: **Improving the pharmacokinetic properties of biologics by fusion to an anti-hsa shark vnar domain.** *mAbs* (2012) **4**(6):673-685.

9. Goodchild SA, Dooley H, Schoepp RJ, Flajnik M, Lonsdale SG: **Isolation and characterisation of ebolavirus-specific recombinant antibody fragments from murine and shark immune libraries.** *Molecular immunology* (2011) **48**(15-16):2027-2037.

10. Nuttall SD, Krishnan UV, Doughty L, Nathanielsz A, Ally N, Pike RN, Hudson PJ, Kortt AA, Irving RA: **A naturally occurring nar variable domain binds the kgp protease from porphyromonas gingivalis.** *FEBS letters* (2002) **516**(1-3):80-86.

11. Nuttall SD, Krishnan UV, Hattarki M, De Gori R, Irving RA, Hudson PJ: **Isolation of the new antigen receptor from wobbegong sharks, and use as a scaffold for the display of protein loop libraries.** *Mol Immunol* (2001) **38**(4):313-326.

12. Dooley H, Flajnik MF, Porter AJ: **Selection and characterization of naturally occurring single-domain (ignar) antibody fragments from immunized sharks by phage display.** *Mol Immunol* (2003) **40**(1):25-33.

13. Ohtani M, Hikima J, Jung TS, Kondo H, Hirono I, Aoki T: **Construction of an artificially randomized ignar phage display library: Screening of variable regions that bind to hen egg white lysozyme.** *Mar Biotechnol (NY)* (2013) **15**(1):56-62.

14. Shao CY, Secombes CJ, Porter AJ: **Rapid isolation of ignar variable single-domain antibody fragments from a shark synthetic library.** *Mol Immunol* (2007) **44**(4):656-665.

15. Kopsidas G, Roberts AS, Coia G, Streltsov VA, Nuttall SD: **In vitro improvement of a shark ignar antibody by qbeta replicase mutation and ribosome display mimics in vivo affinity maturation.** *Immunology letters* (2006) **107**(2):163-168.

16. Nuttall SD, Humberstone KS, Krishnan UV, Carmichael JA, Doughty L, Hattarki M, Coley AM, Casey JL, Anders RF, Foley M, Irving RA *et al*: **Selection and affinity maturation of ignar variable domains targeting plasmodium falciparum ama1.** *Proteins* (2004) **55**(1):187-197.

17. Liu JL, Anderson GP, Goldman ER: **Isolation of anti-toxin single domain antibodies from a semi-synthetic spiny dogfish shark display library.** *BMC biotechnology* (2007) **7**(78.