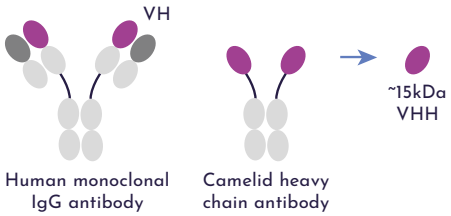
isogenica

ISOXTEND® - Half-life extension for biotherapeutics

Single domain antibodies such as VHH are ideal building blocks for next-generation multi-specific biotherapeutics. They have binding capabilities similar to those of conventional monoclonal antibodies but are typically less immunogenic and can target antigens and epitopes that are considered difficult or intractable for typical antibodies. Their adaptability in formatting and engineering into multiple therapeutic formats, as well as their high thermal stability, make them an essential asset in drug development.



Our VHH-based ISOXTEND® technology protects biotherapeutics from kidney clearance by 'piggybacking' onto the serum albumin endocytic recycling pathway, significantly extending therapeutic half-life.

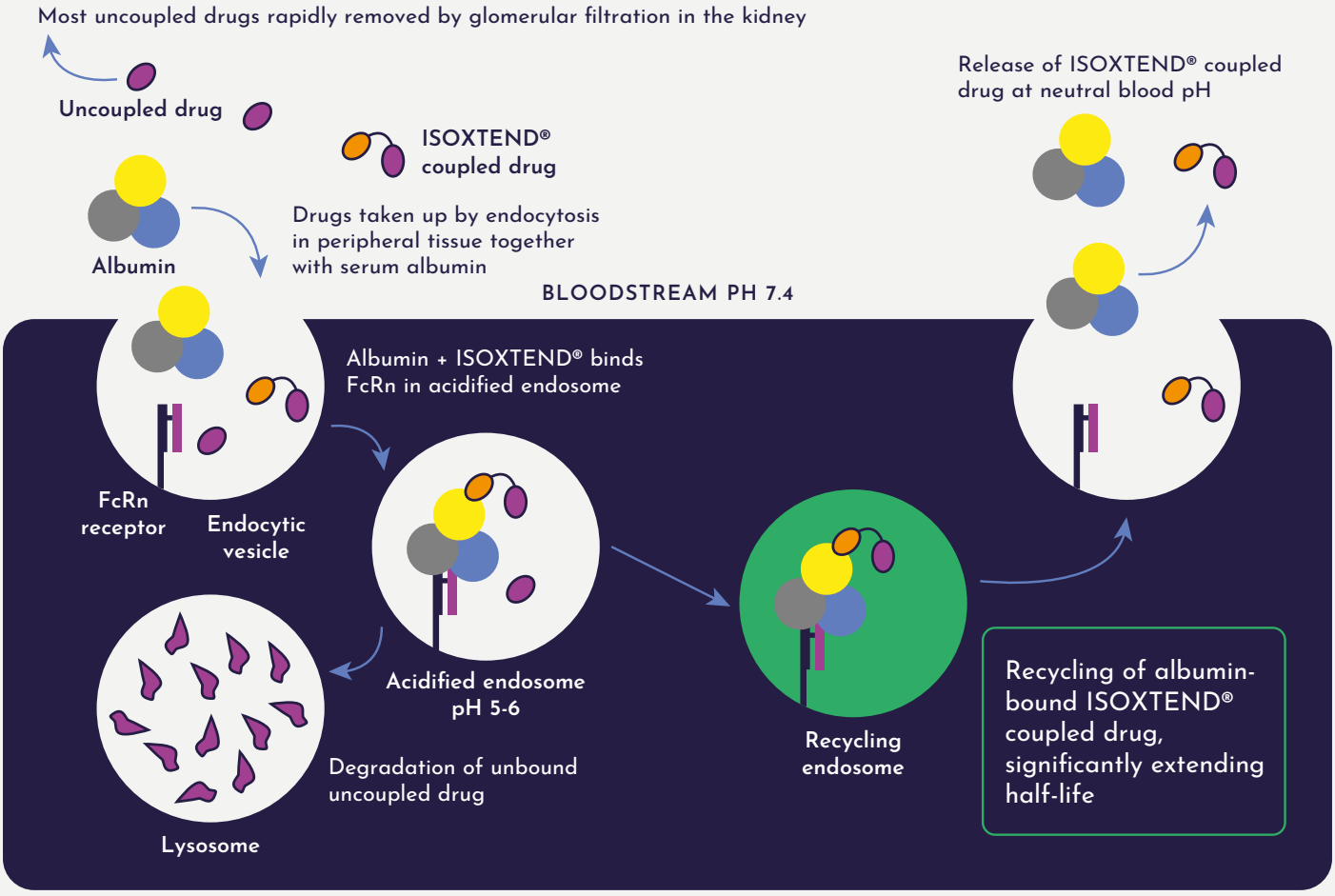


Figure: ISOXTEND® significantly extends drug half-life by protecting biotherapeutics from kidney filtration through utilisation of the endogenous serum albumin endocytic recycling pathway.

- ISOXTEND® is a humanised albumin-binding VHH that extends half-life up to 26 hours in mice, equating to 16-19 days in humans.
- ISOXTEND® is species cross-reactive, facilitating preclinical studies in species including mouse and cynomolgus monkey
- Plug&Play technology allows creation of multi-specific VHH-based antibody therapeutics with novel functionality and significantly increased half-life

ISOXTEND® - A VALUABLE ADDITION TO BIOTHERAPEUTICS

Conventional IgG-based immunotherapies have a long half-life due to recycling through the classic endocytic pathway, mediated by the binding of the antibody Fc domain to the neonatal Fc receptor (FcRn). However, Fc domains can cause toxicity in the liver and have unwanted interactions with immune cells, reducing the potency of IgG-based bi-specifics in solid tumours.

In contrast, current VHH-based therapeutics such as blinatumomab avoid these issues but have a very short half-life in the body due to rapid glomerular filtration in the kidneys, requiring multiple, frequent infusions which limits their use.

Human Serum Albumin (HSA) is the most abundant protein in plasma, with a circulatory half-life of approximately 3 weeks. Enabling drugs to bind to HSA therefore offers the opportunity to enhance their pharmacokinetic properties.

Serum albumin is actively recycled through the endocytic compartment in peripheral tissue by binding to FcRn. Upon endocytosis, acidic pH-dependent binding protects the FcRn:albumin complex from degradation within the endosomal pathway. Albumin is then released back into the bloodstream upon exocytosis and exposure to neutral blood pH.

ISOXTEND® is a humanised VHH antibody that binds to albumin with nanomolar affinity maintained across a wide pH range. This enables the antibody to 'piggyback' through the endocytic recycling compartment, protecting it from clearance by the kidney while maintaining all other functional characteristics (see Figure). ISOXTEND® is cross-reactive with multiple species including mouse and cynomolgus monkey, and increases VHH antibody half-life up to 26 hours in mice, compared with approximately 2 hours for similar drugs without the addition of ISOXTEND®. This translates to an extended half-life in humans between 16 to 19 days.

ISOXTEND®-conjugated molecules can be easily combined with additional VHH antibodies (e.g. TcE or TAA) using Isogenica's Plug&Play platform, creating novel mono-, bi- and or multi-specific biotherapeutics with a significantly extended half-life.

ATTRACTIVE FEATURES OF VHH

- clinically validated
- natural monomer
- high stability and solubility
- no single chain mispairing
- low-immunogenicity
- small size (15kDa, <400 bp)
- high affinity
- easy formatting for versatile applications
- avoids Fc receptor binding

ADDITIONAL BENEFITS OF ISOXTEND®

- FcRn-mediated serum half-life extension
- *in vivo* validated
- multi-species cross-reactivity
- stable and active at endosomal pH
- does not interfere with albumin-FcRn binding

Isogenica is a leading innovator in therapeutic antibody discovery, focused on enabling rapid advancement of next generation antibodies and antibody-based therapeutics into preclinical and clinical studies. Isogenica discovers and develops small-format VHH antibodies that can be linked together to produce multi-specific biotherapeutics for the treatment of cancer, inflammation and other serious diseases. We have a proven track record of partnerships with numerous biotech and biopharma companies from around the world, resulting in the development of several clinical candidates.

WANT TO KNOW MORE?

Get in touch with our business development team:

T +44 1799 533 680

E bd@isogenica.com

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