Proteins containing the Arg-Gly-Asp (RGD) sequence, together with the integrins that serve as receptors for them, play a special role in cell recognition and related processes such as angiogenesis or endothelial apoptosis. RGD related peptides have been and continue to be important tools for research including drug design and development, preparation of radiolabeled derivatives for tumor targeting and imaging, and in novel biomaterials development.

Peptides International has been a key resource for many of these efforts by providing leading edge tools for RGD and broader integrin research to investigators in academia and industry. Technical expertise that we have gained over the years in multiple facets of the RGD field has been integrated into an “RGD Technology Platform” which we hope will facilitate investigators’ customized, ground-breaking research and exciting new discoveries.

**BACKGROUND**

Proteins containing an exposed Arg-Gly-Asp (RGD) sequence have been known for many years to play a special role in cell recognition and related processes such as angiogenesis or endothelial apoptosis. Together, integrins and RGD proteins comprise a versatile cell recognition system controlling crucial events such as cell adhesion, migration, growth, differentiation, and apoptosis. Among the integrin super-family, the $\alpha_v\beta_3$ integrin is highly expressed on activated endothelial cells and tumor cells such as melanoma, glioblastoma and osteosarcoma, and regulates the production of vascular endothelial growth factor (VEGF) in tumor cells required for tumor angiogenesis through activation, clustering, and signaling.

Design of drugs based on the RGD structure that inhibit the $\alpha_v\beta_3$ integrin function has been a focus of intense study for developing new treatments for diseases such as thrombosis, and cancer. For example, the cyclic pentapeptide $\text{cyclo}(\text{RGDf(NMe)V})$, Cilengitide$^\text{TM}$, an inhibitor of $\alpha_v\beta_3$ and $\alpha_v\beta_5$ integrin receptors, is being evaluated as a cancer drug and is currently in phase III clinical trials for treatment of glioblastoma multiforme.

Peptides International is an industry leader for RGD related cyclic and multimeric peptides, conjugates, and custom chemistry services; and is ready to serve the ever-changing and technically challenging needs of investigators in the field.

**Applications and Potential Benefits to Researchers:**
- Integrin related RGD research
- NCEs and cancer drug development
- Useful to prepare radiolabeled agents
- Tumor targeting, imaging and diagnostics
- Novel biomaterial research & development
- Tissue repair and wound healing studies
RGD peptides and mimetics are also useful tools to study integrin functions in various biological systems. Recently, interest in high affinity ligands containing the RGD sequence has intensified in areas such as tumor targeting, molecular imaging and therapy of tumors. 

RGD peptides containing chelating moieties are suitable for these applications due to their compatibility with radiolabeling or chemical modification and their tendency to be less immunogenic than antibodies. Recent reviews describe efforts to develop radiolabeled RGD peptides and related peptidomimetics that show high affinity and selectivity for the $\alpha_v\beta_3$ integrin for tumor targeting. 

Examples include cyclic RGD peptides radiolabeled with $^{18}$F, $^{64}$Cu, $^{68}$Ga for PET, $^{99m}$Tc for SPECT or $^{177}$Lu for therapeutic applications. Among these, $[^{18}\text{F}]$Galacto-RGD and $[^{18}\text{F}]$-AH111585 are currently under clinical investigation.

Studies also indicate dendrimeric RGD conjugates may enhance the delivery of imaging agents that target carcinoma cells and hold promise for siRNA delivery to solid tumors such as glioma. RGD-conjugated hydrogels are being studied as microenvironments for tissue growth and may find applications in wound healing and tissue repair.

Early studies in the design of modulators of integrin function led to the identification of RGDX cyclic pentapeptides, which have been shown to be highly selective to $\alpha_v\beta_3$ integrins. Multivalent molecules containing two to eight cyclic RGD structures showing enhanced affinity and avidity have also been described. Heteromeric structures containing RGD structures hybridized with various biological agents represent another interesting variation in molecular design. Nanoparticles, radionucleotide tracers and bonding agents or spacers, such as polyethylene glycol (PEG) polymers, are also frequently employed in the use of RGD peptides. PEG polymers have become increasingly important in optimizing RGD peptides for specific therapeutic applications. Depending on length, protection, and end groups, these polymers can serve as pharmacokinetic modifiers, linkers to functional groups (e.g., chelating agents, dyes) and spacers to avoid nonspecific interactions with the RGD or to allow multi-cyclic molecules to reach different receptors.

**Components of the RGD Technology Platform**

**Catalog Products**
- Industry-leading collection of RGD peptides
- Analogs, cyclic, multimeric, chelating derivatives, etc
- High purity and ready availability

**Custom Services**
- Chemical route development
- Process scale-up and multi-gram preparations
- Examples of analogs and derivatives:
  - Cyclic and linear RGD molecules
  - Multivalent peptides (dimeric to octameric)
  - Complex organic hybrids
  - Defined length PEG and bifunctional linkers
  - Biotin, fluorophores and chromophores
  - Chelating agents

**RGD TECHNOLOGY PLATFORM**

Peptides International has been a key resource for many of these efforts by providing leading edge tools for RGD and integrin research to investigators in academia and industry. The result has been the establishment of an RGD TECHNOLOGY PLATFORM that integrates our internal expertise in several aspects of RGD chemistry including preparation of complex multimeric derivatives, process development and large scale synthesis, as well as an industry-leading catalog collection of readily available RGD-related products. The primary objective of this platform is to service the ever-changing and technically
CUSTOM CHEMISTRY SERVICES

Peptides International has been and continues to be a primary service provider for confidential custom services to investigators in the field. These services range from chemical route development, to the synthesis of RGD molecules consisting of complex organic structures, small scale synthesis for proof of concept, process scale up and pilot-scale synthesis.

RGD TECHNOLOGY EXPERTISE

Leading the RGD program is PI’s senior scientist Dr. Andrzej Czerwinski, who has synthesized some of the most complex cyclic, multimeric and PEGylated compounds known in the field to date. Dr. Czerwinski, passionate about his interest in this area of research states “we are excited to serve as a micro research center for RGD peptides or to collaborate on any new challenge in this area.”

As a validation of the quality of our products and services, a number of literature publications and patents from leading researchers in the fields of RGD / integrin research, drug discovery, drug delivery, diagnostics and biomaterial research cite Peptides International as the source. For a selected list of citations referencing Peptides International as a resource, please contact us or refer to our website PEPNET.COM.
REFERENCES

34. For more about Dr. Czerwinski, see PEPNET, Vol. 21, Issue No. 2

ABOUT PEPTIDES INTERNATIONAL

Peptides International is an established (~25 years) USA-based provider of catalog products and custom chemistry services specializing in biologically active peptides, glyco-conjugates, defined-length PEGylations, enzyme substrates (FRET, MCA, pNA) and inhibitors, amino acid derivatives, combinatorial peptide libraries, and a variety of resins and reagents.

The PI Louisville facility consists of administrative and business offices, fully equipped quality control laboratories, a quality assurance department, and multiple self-contained laboratory suites each with hood and necessary supporting equipment. In addition there are pilot-scale production suites with walk-in hoods, jacketed reactors, evaporators, filtration and other equipment etc., up to 100L capacity. Purification of custom produced products is carried out by conventional techniques such as solvent-solvent extractions, crystallizations, and by preparative chromatographic instrumentation – column sizes to 110mm diameter – suitable for ion-exchange, flash-chromatography and reverse phase HPLC methodologies.

Please contact us to discuss how Peptides International technologies and services could address your specific needs.